

1 **Practice patterns of medications for patients with malignant**
2 **bowel obstruction using a nationwide claims database and the**
3 **association between treatment outcomes and concomitant use**
4 **of H₂-blockers/proton pump inhibitors and corticosteroids**
5 **with octreotide**

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7 Takaaki Minoura, MD, MPH¹, Masato Takeuchi, MD, MPH¹, Tatsuya Morita, MD²,

8 Koji Kawakami, MD, PhD¹

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10 *1 Department of Pharmacoepidemiology, Graduate School of Medicine and Public*

11 *Health, Kyoto University, Yoshida Konoecho, Sakyo, Kyoto, Japan,*

12 *2 Palliative and Supportive Care Division, Seirei Mikatahara General Hospital,*

13 *Hamamatsu, Japan*

14

15 *Address correspondence to:* Koji Kawakami, MD, PhD, Department of

16 *Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto*

17 *University, Yoshida Konoecho, Sakyo, Kyoto, Japan*

18 *Tel: +81-75-753-9469*

19 Fax: +81-75-753-4469

20 E-mail: kawakami.koji.4e@kyoto-u.ac.jp

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22 ABSTRACT

23 **Context.** Malignant bowel obstruction (MBO) impairs the quality of life in patients
24 with advanced cancer. Octreotide, acid-suppressing medications such as H₂-receptor
25 antagonists (H₂ blockers) and proton pump inhibitors (PPIs), and corticosteroids are
26 often used in combination for symptom control.

27 **Objectives.** We evaluated the practice patterns of medications for patients hospitalized
28 with MBO using a large claims database in Japan. Additionally, we explored the
29 association of adding H₂-blockers/PPIs or corticosteroids to octreotide on treatment
30 outcomes.

31 **Methods.** We analyzed data from a nationwide medical claims database from April
32 2010 to March 2015 containing 975,000 patients. We included all adult inpatients with
33 cancer who used octreotide 300 µg/day or more and summarized each patient's
34 medication use. We also assessed whether concomitant use of H₂-blockers/PPIs or
35 corticosteroids was associated with the number of days of nasogastric tube (NGT)
36 insertion; logistic regression was used to adjust the patients' baseline factors.

37 **Results.** We included 3,090 patients; octreotide alone was used in 1,649 (53%) cases. A
38 combination of octreotide and H₂-blockers or PPIs was used in 419 and 337 cases (14%
39 and 11%), respectively; a combination of octreotide and corticosteroids was used in 374

40 cases (12%). Of the 1,595 patients who underwent NGT insertion, those using
41 corticosteroids with octreotide had a higher odds ratio (OR) of NGT removal within 4
42 days of insertion (adjusted OR=1.16; 95% confidence interval = 1.08–1.23).

43 **Conclusion.** Octreotide alone was used in the majority of patients, and the concomitant
44 use of corticosteroids was more likely to be associated with early NGT removal.

45

46 (250/250 words)

47

48 **Key words**

49 Malignant bowel obstruction, octreotide, corticosteroid, claims database, palliative care,
50 concomitant drugs

51

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53 **Running title**

54 Medications for malignant bowel obstruction

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58 INTRODUCTION

59 Malignant bowel obstruction (MBO) is a common complication in patients with
60 advanced cancer with an incidence of 3%–15% (1-6). Symptoms include abdominal
61 pain, colic, nausea, vomiting, and abdominal swelling; these symptoms markedly impair
62 the patients' quality of life (1-6). While surgical treatment can be a treatment option for
63 some patients with MBO, a pharmacological approach is principally used in palliative
64 care settings (1-6). Key medications include octreotide, acid-suppressing medications
65 such as H₂-receptor antagonists (H₂ blockers) and proton pump inhibitors (PPIs), and
66 corticosteroids (1-6). Existing empirical studies suggest octreotide (7-11), acid-
67 suppressing medications such as H₂ blockers and PPIs (12, 13), and corticosteroids (14-
68 16) are effective in alleviating the symptoms of MBO, but a recent randomized
69 controlled trial revealed that octreotide administration demonstrated no additional
70 benefit for patients who received H₂ blockers/PPIs, corticosteroids, and
71 butylscopolamine as part of their standard treatment (17). In clinical settings, these
72 medications are commonly used in combination, and it is important to explore the
73 current practice of drug combination in patients with MBO and the association between
74 treatment outcomes and drug combinations (6). To date, however, no nationwide studies
75 have examined how these drugs are used in actual clinical settings. Examining the

76 treatment effects of drugs in actual clinical settings, not only in clinical trials, is
77 valuable for the interpretation of research findings (18,19).

78 Thus, the primary aim of this study was to describe the practice patterns of
79 medications for patients hospitalized with MBO using a nationwide claims database. The
80 secondary aim was to explore the association of adding H₂-blockers/PPIs or
81 corticosteroids to octreotide on treatment outcomes.

82

83 METHODS

84 This study was a database analysis using nationwide claims data from about 10 million
85 patients in Japan. The study was approved by the ethics committee of Kyoto University
86 and the need for informed consent was waived because of the use of anonymous data only.

87

88 Data Sources

89 This study was conducted using the Japanese Medical Data Vision database, a
90 commercial, electronic, record-based healthcare database. This database contains
91 patient-level information on demographic characteristics, diagnoses coded according to
92 the International Classification of Diseases, 10th revision (ICD-10), clinical data, and
93 prescription information such as dose, quantity, and number of days of supply. The

94 database contains data on inpatient and outpatient medical care from a panel of 192
95 hospitals distributed in different regions throughout Japan and includes 975,000
96 patients. The age and sex distribution of the patients in the database is similar to that of
97 the national demographic profile of individuals seeking healthcare (20). Patient
98 identities were encrypted for protection of privacy.

99

100 Case Definition

101 All patients recorded in the database from April 2010 to March 2015 were screened. No
102 specific ICD-10 codes for MBO existed, and our primary aim was to investigate how
103 octreotide was used in the palliative care of cancer patients; thus, we decided to include
104 adult inpatients with a diagnosis of intraabdominal cancers, i.e., cancers of the esophagus,
105 stomach, small and large intestine, liver, pancreas, bile duct system, or ovary, who used
106 octreotide 300 µg/day or more. We excluded patients who received once-a-month
107 octreotide because it was reasonably assumed that the monthly type somatostatin analog
108 was used for endocrine disease. We also excluded patients who underwent surgical
109 management including stenting or percutaneous endoscopic gastrostomy (PEG). We also
110 excluded patients who had other primary tumor sites and those who did not have a
111 diagnosis recorded.

112 Outcome Measures

113 The main outcome measure was the prescription patterns of drugs used concomitantly
114 with octreotide, i.e., the number of patients who received H₂ blockers/PPIs and
115 corticosteroids. We also recorded the use of butylscopolamine. We defined the first
116 octreotide prescription day as the index day for each patient and identified any
117 concomitant drugs that were used on the index day. To extract information on concomitant
118 drugs, we limited the search to drugs using the Anatomical Therapeutic Chemical
119 Classification System (Supplemental Table 1), a drug classification system defined by the
120 World Health Organization. If such medications were administered on the index day, we
121 judged that there was concomitant use regardless of the period. For corticosteroids,
122 generic names and prescription period were also recorded. We calculated the daily
123 hydration volume of the index day and classified it as less than 1000 ml/day or 1000
124 mL/day or more.

125 As a secondary endpoint, for the subgroup of patients who had undergone
126 nasogastric tube (NGT) insertion on the index day, we calculated the total number of days
127 of NGT insertion. Although we believe that patient-reported outcomes such as intensity
128 of nausea or frequency of vomiting are important, such data was unavailable in the claims
129 database. Therefore, we decided to use claims data of NGT as a surrogacy outcome. The

130 total number of days of NGT insertion was calculated from the first day when the patient
131 received octreotide (index day) to the day before the end of the NGT insertion or the day
132 the patient died or was discharged. Claims data recorded NGT insertion once daily as
133 long as it remained in place. In addition, information about disease-specific variables,
134 including age, sex, primary sites of cancer, clinical department, and length of hospital
135 stay was obtained.

136

137 Statistical analyses

138 Patterns and frequency of drug administration are presented as numbers with percentages.
139 For the secondary endpoint, we analyzed the patients who had undergone NGT insertion
140 on the index day. Initially, we compared the NGT period (days) among the groups of
141 octreotide alone, octreotide plus H₂-blockers, octreotide plus PPIs, octreotide plus
142 corticosteroids, and octreotide plus H₂-blockers/PPIs plus corticosteroids. We used the
143 Wilcoxon rank sum test. Second, we calculated the adjusted odds ratio (OR) for the days
144 of NGT removal using logistic regression analysis. The OR was calculated using the
145 patients who received octreotide alone as a reference and was adjusted by sex, age,
146 hydration volume, use of butylscopolamine, and type of cancer. Additional analysis was
147 performed to confirm the robustness of the results: 1) we divided the period of NGT

148 insertion into 3 groups as follows: NGT removed within 4 days, within 7 days, and after
149 more than 14 days; 2) we performed subgroup analyses on patients with different
150 hydration volumes (<1000 mL/day vs. 1000 mL/day or more, 1000 mL/day or less vs.
151 more than 1000 mL/day, and <1500 mL/day vs. 1500 mL/day or more); and 3) we
152 performed subgroup analyses on patients with and without butylscopolamine use.
153 Because of the exploratory nature of this study, a p-value <0.05 was considered
154 statistically significant. Analyses were performed using SAS, version 9.4 (SAS Institute,
155 Cary, NC).

156

157 RESULTS

158 *Baseline Characteristics*

159 Of the 6,495 patients who used octreotide, a total of 3,090 patients met our study
160 eligibility criteria (Fig. 1). Table 1 shows the baseline characteristics of the patients. The
161 mean age of the patients was 67 years, and stomach cancer was the most prevalent type
162 of cancer. A hydration volume of 1000 ml/day or more was observed in 1,720 (56%) cases.
163 The median of hydration volume was 1000 ml/day (interquartile range [IQR]: 500-1365).
164 A total of 1,595 (52%) patients who underwent NGT insertion were identified. Among
165 them, 1,016 patients (76%) survived for the entire study period, and the median number
166 of days that each patient survived was 11 days. Butylscopolamine was used in 4.4% of

167 the cases.

168

169

170 *Patterns and frequency of drug administration*

171 Octreotide was used without H₂-blockers/PPIs or corticosteroids in 1,649 (53%) cases

172 (Table 2). A combination of octreotide and H₂-blockers and PPIs was observed in 419 and

173 337 cases (14% and 11%), respectively; and a combination of octreotide and

174 corticosteroids was observed in 374 (12%) cases. Types of corticosteroids were:

175 dexamethasone in 206 cases (55%), betamethasone in 116 cases (31%), prednisolone in

176 11 cases (5.1%), and others in 22 (5.9%) cases.

177

178 *Association of drug combinations on NGT removal*

179 The 1,595 patients who had undergone NGT insertion were included in this subgroup

180 analysis (52%). In univariate analysis, patients treated with corticosteroids had a

181 significantly shorter median period of NGT insertion than those who did not use

182 corticosteroids (9 vs. 13 days, $P<0.001$; Table 3). After adjusting for sex, age, hydration

183 volume, use of butylscopolamine, and type of cancer, the results were unchanged; the

184 combined use of corticosteroids with octreotide was associated with a shorter period of

185 NGT insertion (Table 4). Patients using corticosteroids with octreotide had a higher OR
186 of removal within 4 days (adjusted OR=1.16; 95% CI=1.08–1.23) and 7 days (adjusted
187 OR=1.14; 95% CI=1.07–1.21) and a lower OR of NGT retention after 14 days (adjusted
188 OR=0.86; 95% CI=0.81–0.91).

189 Subgroup analyses on patients with a hydration volume of <1000 mL/day and
190 1000 mL/day or more revealed the essentially same results (Supplemental Table 2).
191 Sensitivity analyses using different cut-off points (i.e., ≤1000 mL vs. 1000 mL<, <1500
192 mL vs. ≤1500 mL) and subgroup analyses on the patients with or without the use of
193 butylscopolamine achieved the same results (data not shown).

194

195 DISCUSSION

196 MBO is relatively common in palliative care settings, but to date, few studies have
197 identified the drug combination profiles administered to patients with MBO in actual
198 clinical settings (21). In this study, we revealed that use of octreotide alone was the most
199 common (53%), followed by octreotide in combination with H2 blockers/PPIs (14/11%),
200 and corticosteroids (12%). This finding suggests that, although a combination of H2
201 blockers/PPIs and corticosteroids is recommended for palliative treatment of MBO (1-6),
202 octreotide is currently more likely to be used without these medications. Further studies

203 from other countries will be valuable to obtain further insights into current practices in
204 the management of MBO.

205 We defined the length of NGT insertion as a surrogate marker for medical
206 treatment, revealing that the length of insertion was significantly shorter in the group
207 using corticosteroids in combination with octreotide. Patients who had been administered
208 corticosteroids were more likely to undergo early NGT removal. This may be
209 pharmacologically plausible because the anti-inflammatory effect leads to the reopening
210 of the bowel occlusion owing to reduction of the edema caused by the tumor (14). A trend
211 toward an early resolution of obstructions with the combined use of octreotide and
212 corticosteroids supports the conclusion of the existing meta-analysis of clinical trials (14).
213 In patients receiving octreotide, the addition of corticosteroids may be more effective in
214 palliating symptoms of MBO. Some clinicians have concerns that the use of
215 corticosteroids is associated with serious side effects such as infection, hyperglycemia,
216 and psychiatric complications (14). However, the overall frequency of such side effects
217 was estimated to be low in previous studies (22,24). As there is still uncertainty regarding
218 both the benefits and potentially harmful effects of corticosteroids for MBO, the benefit
219 of corticosteroids for MBO should be further evaluated in comprehensive outcomes in
220 both clinical trials and real-world studies. We found that 48% of our patients were

221 managed without NGT. Thus, the pharmacological management of those patients is
222 relatively important.

223 Of note, a combination of acid-reducing agents such as H2 blockers/PPIs and
224 octreotide resulted in prolonged NGT administration as compared with octreotide alone.
225 The potential interpretation is that patients with obstruction of the upper intestines were
226 more likely to receive acid-reducing agents and were less likely to experience the benefits
227 of octreotide (24). Further studies are necessary to confirm why the use of acid-reducing
228 agents is associated with poor outcomes in patients with MBO.

229 This study has several strengths. First, the study was designed based on real-
230 world clinical settings using a nation-wide database. Second, NGT removal was used as
231 a surrogacy index of symptoms such as nausea and vomiting. This outcome is objective.
232 Nonetheless, this study had several limitations. First, MBO occurs more frequently in
233 patients with advanced cancer (5), but this database obtained no data about the clinical
234 stage of cancer. Second, the side effects of corticosteroids were not investigated in this
235 study. Although corticosteroids were associated with a shorter duration of NGT insertion,
236 it is unclear whether this benefit outweighed the adverse effects of corticosteroids; thus,
237 further studies addressing these issues are warranted. Third, the definition of concomitant
238 use was based on only the index day, and differences in the timing of administration and

239 MBO severity was not investigated. Finally, this database contained no data about the
240 reasons for NGT insertion and removal. Although we believe it is reasonable to regard
241 NGT removal as an index of improvement because surgical patients were excluded, our
242 results should be interpreted with caution because of the nature of this study.

243 In summary, we found that octreotide alone was used in the majority of patients,
244 and use of corticosteroids was more likely to be associated with early NGT removal.
245 Further clinical trials and observational studies are needed to clarify the role of drug
246 combinations in managing MBO.

247

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252

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Table 1. Baseline characteristics (N=3,090 patients)

Age, mean (SD)		67 (11.8)
Sex, N (%)	Male	1,758 (57)
	Female	1,332 (43)
Primary sites of cancer, N (%)	Stomach	1042 (33)
	Large intestine	813 (26.3)
	Pancreas	579 (18.7)
	Bile duct system	285 (9.2)
	Ovary	208 (6.7)
	Esophagus	94 (3.0)
	Liver	64 (2.1)
	Small intestine	5 (0.2)
Clinical department, N (%)	Surgery	1,711 (55)
	Internal medicine	998 (32)
	Gynecology	161 (5)
	Palliative medicine	32 (1)
	Others	188 (6)
Length of stay, median (IQR)		30 (15–54)
Use of butylscopolamine (%)		135 (4.4)
Hydration volume, N (%)	<1000 ml/day	1,370 (44)
	1000 ml/day or more	1,720 (56)

SD: standard deviation; IQR: interquartile range

Table 2. Drug prescription patterns (N=3,090 patients)

Combinations	<i>N</i>	%	95% CI
Octreotide	1649	53	52 – 55
Octreotide + H2 blockers	419	14	12 – 15
Octreotide + Corticosteroid	374	12	11 – 13
Octreotide + PPIs	337	11	10 – 12
Octreotide + Corticosteroid + H2 blockers	141	4.6	4.0 – 5.0
Octreotide + Corticosteroid + PPIs	95	3.1	2.0 – 4.0
Octreotide + PPIs + H2 blockers	65	2.1	2.0 – 3.0
Octreotide + PPIs + H2 blockers + Corticosteroid	10	0.3	0.1 – 0.5

95% CI: 95% confidence interval; H2 blockers: Histamine H2 – receptor antagonist; PPIs: proton pump inhibitors

Table 3. Number of patients with concomitant drugs and days with NGT (N=1,595)

	Period of NGT ^a (IQR ^b)	<i>P</i> value ^c
H2 blockers		
use (n=390)	13 (4–28)	0.49
no use (n=1205)	12 (5–27)	
PPIs		
use (n=328)	14 (7–27.8)	0.04
no use (n=1267)	12 (4–27)	
Corticosteroid		
use (n=211)	9 (4–19)	<0.001
no use (n=1384)	13 (5–29)	
H2 blockers/PPIs+ Corticosteroid		
use (n=101)	9 (4–19)	0.01
no use (1494)	12 (5–28)	

NGT: nasogastric tube; H2 blockers: Histamine H2 – receptor antagonist; PPIs: proton pump inhibitors; ^ain days; ^bIQR: interquartile range; ^cWilcoxon rank sum test (unadjusted)

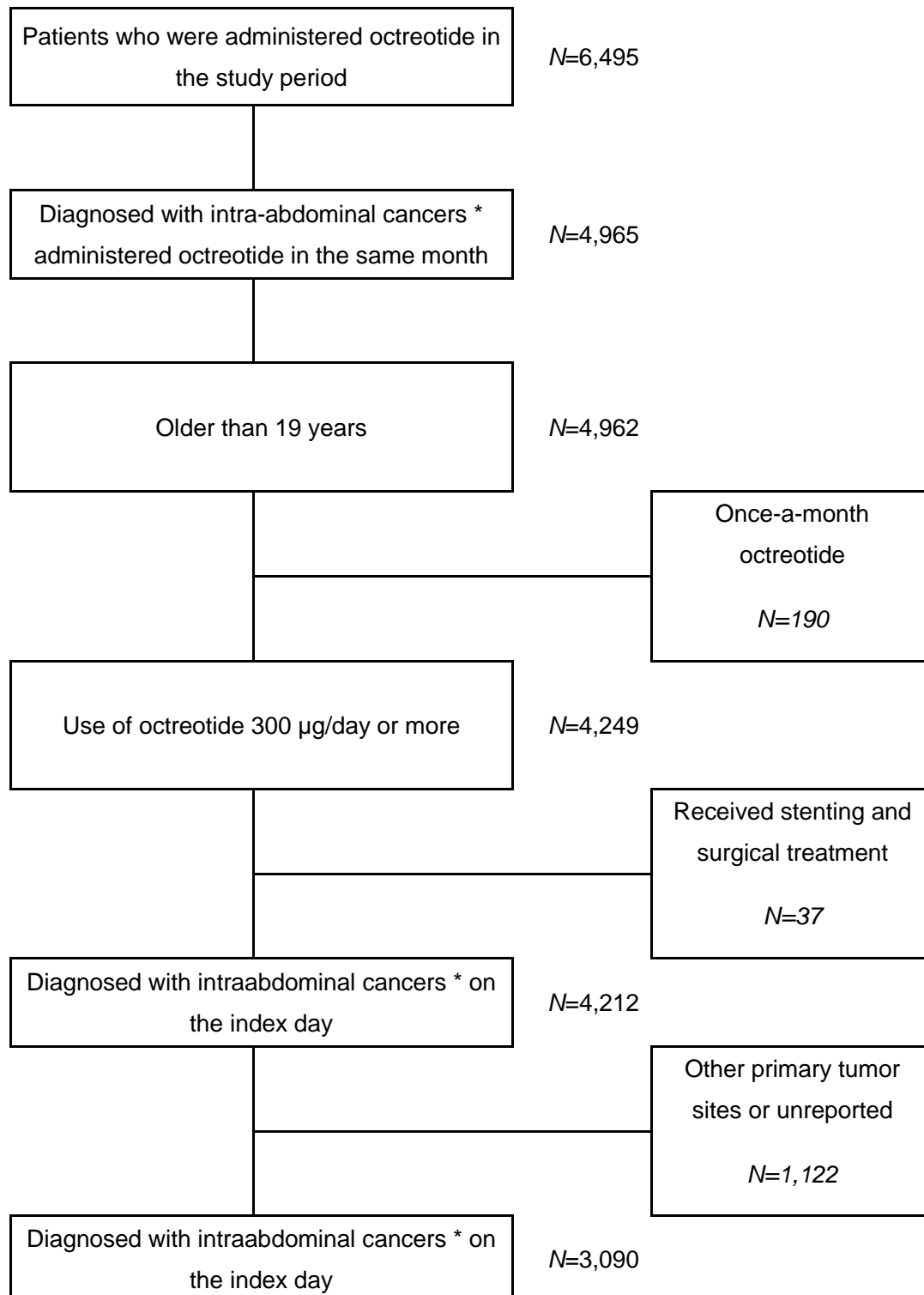
Table 4. Association of concomitant medications (N=1,595)

	NGT removal within 4 days			NGT removal within 7 days			NGT in place for more than 14 days					
	Odds ratio ^a	95% CI		<i>P</i> value	Odds ratio ^a	95% CI		<i>P</i> value	Odds ratio ^a	95% CI		<i>P</i> value
Octreotide alone (n=666)	1.0(reference)				1.0(reference)				1.0(reference)			
Octreotide + H2 blocker (n=390)	0.89	0.83	0.95	0.001	0.89	0.83	0.94	0.0002	1.05	0.99	1.11	0.11
Octreotide + PPI (n=328)	0.84	0.78	0.90	<.0001	0.83	0.78	0.89	<.0001	1.07	1.01	1.14	0.02
Octreotide + Corticosteroid (n=211)	1.16	1.08	1.23	<.0001	1.14	1.07	1.21	<.0001	0.86	0.81	0.91	<.0001

NGT: nasogastric tube; OR: odds ratio; 95% CI: 95% confidence interval; H2 blockers: Histamine H2 – receptor antagonist; PPIs: proton pump inhibitors

^aMultivariate analyses adjusted for sex, age, hydration volume, use of butylscopolamine and type of cancer

Figure 1. Flow diagram of the selection of study individuals



*: Esophagus, Stomach, Small and Large intestine, Liver, Pancreas, Bile duct system, or Ovarian cancer

Supplemental Table 1. Concomitant Drugs and Anatomical Therapeutic Chemical

Classification System (ATC code)

ATC name	ATC code	Representative drug
Antigrowth hormone	H01C2	Octreotide
Butylscopolamine	A03A0	Butyl scopolamine bromide
Histamine H2-receptor antagonist	A02B1	Cimetidine
		Nizatidine
		Famotidine
		Ranitidine
Proton pump inhibitor	A02B2	Omeprazole
		Rabeprazole
		Lansoprazole
Corticosteroid	H02A1	Dexamethasone
		Betamethasone
		Prednisolone
		Methylprednisolone
		Hydrocortisone succinate

Supplemental Table 2. Association of concomitant medications by hydration volume

<1000 ml (N=683)

	NGT removal within 4 days			NGT removal within 7 days			NGT in place for more than 14 days		
	Odds ratio	95% CI	<i>P</i> value	Odds ratio	95% CI	<i>P</i> value	Odds ratio	95% CI	<i>P</i> value
Octreotide alone (n=212)	1.0(reference)			1.0(reference)			1.0(reference)		
Octreotide + H2 blocker (n=214)	0.89	0.80 0.98	0.018	0.90	0.82 0.99	0.03	1.06	0.97 1.15	0.18
Octreotide + PPI (n=196)	0.94	0.84 1.04	0.24	0.93	0.84 1.03	0.18	1.05	0.96 1.15	0.28
Octreotide + Corticosteroid (n=61)	1.14	1.04 1.26	0.005	1.11	1.01 1.21	0.03	0.90	0.83 0.97	0.01

NGT: nasogastric tube; OR: odds ratio; 95% CI: 95% confidence interval; H2 blockers: Histamine H2 – receptor antagonist; PPIs: proton pump inhibitors

^aMultivariate analyses adjusted for sex, age, use of butylscopolamine and type of cancer

≥1000 ml (N=912)

	NGT removal within 4 days			NGT removal within 7 days			NGT in place for more than 14 days		
	Odds ratio	95% CI	<i>P</i> value	Odds ratio	95% CI	<i>P</i> value	Odds ratio	95% CI	<i>P</i> value
Octreotide alone (n=454)	1.0(reference)			1.0(reference)			1.0(reference)		
Octreotide + H2 blocker (n=176)	0.91	0.83 0.99	0.035	0.89	0.81 0.97	0.0060	1.04	0.96 1.13	0.35
Octreotide + PPI (n=132)	0.80	0.73 0.87	<0.0001	0.79	0.72 0.86	<0.0001	1.09	1.00 1.18	0.06
Octreotide + Corticosteroid (n=150)	1.17	1.07 1.27	<0.0001	1.18	1.08 1.28	<0.0001	0.83	0.77 0.90	<0.0001

NGT: nasogastric tube; OR: odds ratio; 95% CI: 95% confidence interval; H2 blockers: Histamine H2 – receptor antagonist; PPIs: proton pump inhibitors

^aMultivariate analyses adjusted for sex, age, use of butylscopolamine and type of cancer