Practice patterns of medications for patients with malignant bowel obstruction using a nationwide claims database and the association between treatment outcomes and concomitant use of H_2-blockers/proton pump inhibitors and corticosteroids with octreotide

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ABSTRACT

Context. Malignant bowel obstruction (MBO) impairs the quality of life in patients with advanced cancer. Octreotide, acid-suppressing medications such as H_2-receptor antagonists (H_2 blockers) and proton pump inhibitors (PPIs), and corticosteroids are often used in combination for symptom control.

Objectives. We evaluated the practice patterns of medications for patients hospitalized with MBO using a large claims database in Japan. Additionally, we explored the association of adding H_2-blockers/PPIs or corticosteroids to octreotide on treatment outcomes.

Methods. We analyzed data from a nationwide medical claims database from April 2010 to March 2015 containing 975,000 patients. We included all adult inpatients with cancer who used octreotide 300 μg/day or more and summarized each patient's medication use. We also assessed whether concomitant use of H_2-blockers/PPIs or corticosteroids was associated with the number of days of nasogastric tube (NGT) insertion; logistic regression was used to adjust the patients' baseline factors.

Results. We included 3,090 patients; octreotide alone was used in 1,649 (53%) cases. A combination of octreotide and H_2-blockers or PPIs was used in 419 and 337 cases (14% and 11%), respectively; a combination of octreotide and corticosteroids was used in 374

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

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

(250/250 words)

Key words

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

Running title

Medications for malignant bowel obstruction

INTRODUCTION

Malignant bowel obstruction (MBO) is a common complication in patients with advanced cancer with an incidence of 3%–15% (1-6). Symptoms include abdominal pain, colic, nausea, vomiting, and abdominal swelling; these symptoms markedly impair the patients' quality of life (1-6). While surgical treatment can be a treatment option for some patients with MBO, a pharmacological approach is principally used in palliative care settings (1-6). Key medications include octreotide, acid-suppressing medications such as H_2-receptor antagonists (H_2 blockers) and proton pump inhibitors (PPIs), and corticosteroids (1-6). Existing empirical studies suggest octreotide (7-11), acid-suppressing medications such as H_2 blockers and PPIs (12, 13), and corticosteroids (14-16) are effective in alleviating the symptoms of MBO, but a recent randomized controlled trial revealed that octreotide administration demonstrated no additional benefit for patients who received H_2 blockers/PPIs, corticosteroids, and butylscopolamine as part of their standard treatment (17). In clinical settings, these medications are commonly used in combination, and it is important to explore the current practice of drug combination in patients with MBO and the association between treatment outcomes and drug combinations (6). To date, however, no nationwide studies have examined how these drugs are used in actual clinical settings. Examining the

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

Thus, the primary aim of this study was to describe the practice patterns of medications for patients hospitalized with MBO using a nationwide claims database. The secondary aim was to explore the association of adding H_2-blockers/PPIs or corticosteroids to octreotide on treatment outcomes.

METHODS

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

Data Sources

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

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

Case Definition

All patients recorded in the database from April 2010 to March 2015 were screened. No specific ICD-10 codes for MBO existed, and our primary aim was to investigate how octreotide was used in the palliative care of cancer patients; thus, we decided to include adult inpatients with a diagnosis of intraabdominal cancers, i.e., cancers of the esophagus, stomach, small and large intestine, liver, pancreas, bile duct system, or ovary, who used octreotide 300 μg/day or more. We excluded patients who received once-a-month octreotide because it was reasonably assumed that the monthly type somatostatin analog was used for endocrine disease. We also excluded patients who underwent surgical management including stenting or percutaneous endoscopic gastrostomy (PEG). We also excluded patients who had other primary tumor sites and those who did not have a 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 H_2 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

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

Statistical analyses

Patterns and frequency of drug administration are presented as numbers with percentages. For the secondary endpoint, we analyzed the patients who had undergone NGT insertion on the index day. Initially, we compared the NGT period (days) among the groups of octreotide alone, octreotide plus H_2-blockers, octreotide plus PPIs, octreotide plus corticosteroids, and octreotide plus H_2-blockers/PPIs plus corticosteroids. We used the Wilcoxon rank sum test. Second, we calculated the adjusted odds ratio (OR) for the days of NGT removal using logistic regression analysis. The OR was calculated using the patients who received octreotide alone as a reference and was adjusted by sex, age, hydration volume, use of butylscopolamine, and type of cancer. Additional analysis was 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

the cases.

Patterns and frequency of drug administration

Octreotide was used without H_2-blockers/PPIs or corticosteroids in 1,649 (53%) cases (Table 2). A combination of octreotide and H_2-blockers and PPIs was observed in 419 and 337 cases (14% and 11%), respectively; and a combination of octreotide and corticosteroids was observed in 374 (12%) cases. Types of corticosteroids were: dexamethasone in 206 cases (55%), betamethasone in 116 cases (31%), prednisolone in 11 cases (5.1%), and others in 22 (5.9%) cases.

Association of drug combinations on NGT removal

The 1,595 patients who had undergone NGT insertion were included in this subgroup analysis (52%). In univariate analysis, patients treated with corticosteroids had a significantly shorter median period of NGT insertion than those who did not use corticosteroids (9 vs. 13 days, $P<0.001$; Table 3). After adjusting for sex, age, hydration volume, use of butylscopolamine, and type of cancer, the results were unchanged; the combined use of corticosteroids with octreotide was associated with a shorter period of

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

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

DISCUSSION

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

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

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

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

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

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

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

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

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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	*N*	%	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])	*P* 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; [a]in days; [b]IQR: interquartile range; [c]Wilcoxon rank sum test (unadjusted)

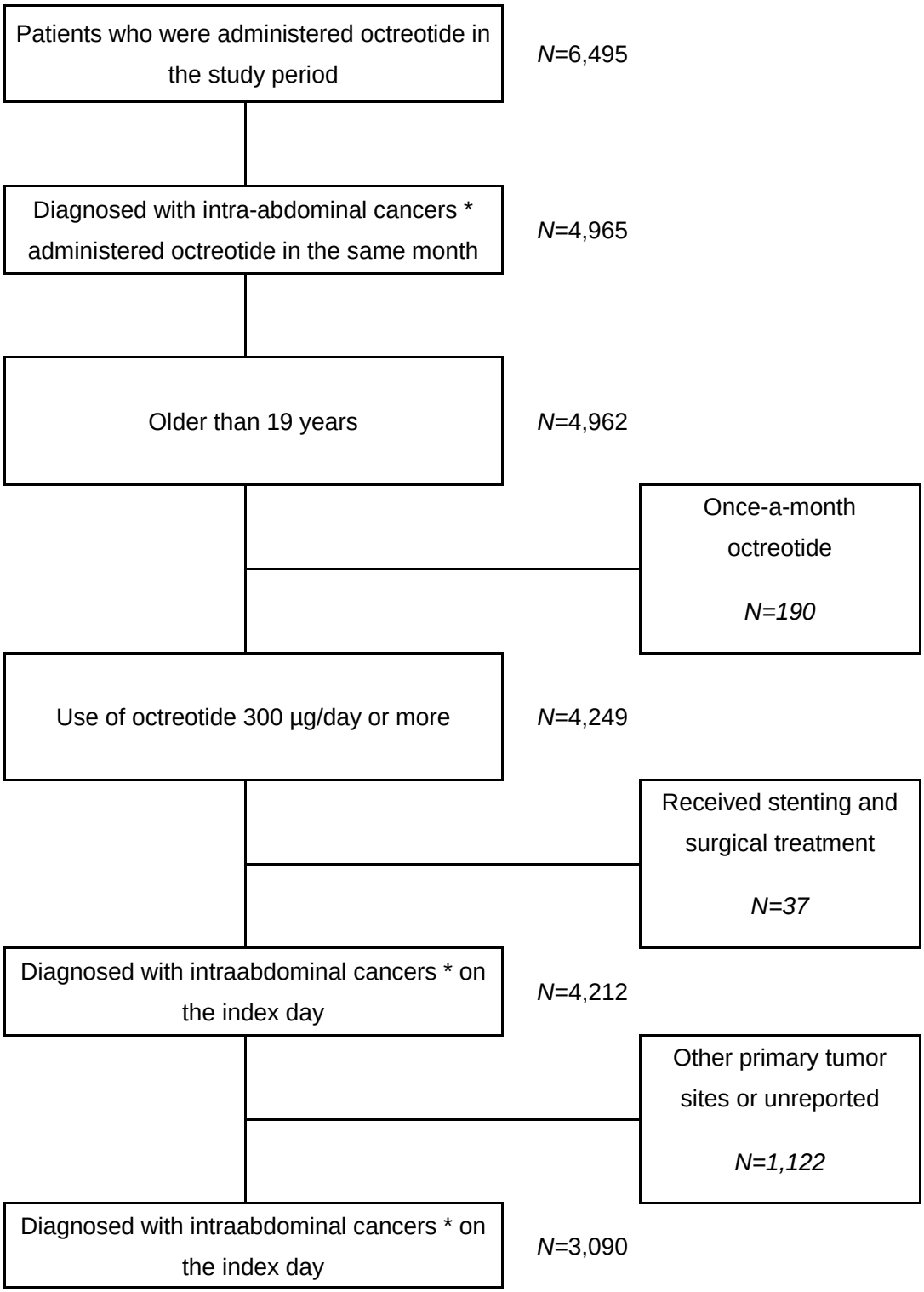
Table 4. Association of concomitant medications (*N*=1,595)

	NGT removal within 4 days				NGT removal within 7 days				NGT in place for more than 14 days			
	Odds ratio[a]	95% CI		*P* value	Odds ratio[a]	95% CI		*P* value	Odds ratio[a]	95% CI		*P* 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

[a]Multivariate 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		*P* value	Odds ratio	95% CI		*P* value	Odds ratio	95% CI		*P* 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

[a]Multivariate 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		*P* value	Odds ratio	95% CI		*P* value	Odds ratio	95% CI		*P* 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

[a]Multivariate analyses adjusted for sex, age, use of butylscopolamine and type of cancer