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The incidence of non-ampullary duodenal cancer in Japan: The first analysis of a national cancer registry

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Abstract

Background and Aim: Although duodenal cancer is rare, no epidemiological research on this disease has been conducted in Asian countries. We aimed to elucidate the incidence and clinical features of duodenal cancer in Japan using a large-scale national database.

Methods: Data of patients with primary duodenal cancer diagnosed from January 1, 2016, to December 31, 2016, were extracted from the Japanese national cancer registry. Excluding malignant neoplasm of the Vater's ampulla, we calculated the incidence among the population as a crude number of patients with duodenal cancer divided by the total Japanese population in 2016. We performed multivariate analyses using logistic regression models to identify risk factors for advanced cancer, defined as metastatic cancer or local invasion to adjacent organs.

Results: Data on 3005 patients were included. The incidence of duodenal cancer was 23.7 per 1 000 000 person-years. In total, 56.4% of cases were detected at the localized stage. In the localized cancer group, endoscopic resection was more frequently performed (48.0%), whereas in the advanced cancer group, surgery and chemotherapy were the major treatment options (39.3% and 41.5%, respectively). Multivariate analyses identified age ≥80 years (odds ratio [OR], 1.489; 95% confidence interval [CI], 1.113–1.992; $P = 0.007$), incidental detection (OR, 2.325; CI, 1.623–3.331; $P < 0.0001$), and precise examination for symptomatic patients (OR, 10.561; CI, 7.416–15.042; $P < 0.0001$) as independent risk factors for advanced cancer.

Conclusions: Our study revealed the incidence of duodenal cancer in Japan. However, localized cancer was the major tumor stage at detection, resulting in a high rate of endoscopic resection.

Introduction

The duodenum is the most proximal portion of the small intestine, which exhibits several distinctive histological features owing to its direct continuity with the pylorus and exposure to gastric juice, pancreatic juice, and bile.[1] Although the incidence of cancer of the small intestine is low, the duodenum is the most frequently involved region.[2–4] Furthermore, most patients with duodenal cancer are diagnosed at an advanced stage, resulting in a poor prognosis.[5–7] With advances in endoscopic equipment and increasing awareness of duodenal tumors, attention to this field has been increasing worldwide.[8–12] The number of patients with duodenal cancer has been gradually increasing.[6,13] However, no epidemiological research on this disease has been conducted in Asian countries.

The Japanese national cancer registry was launched in January 2016 according to the cancer registry promotion law to obtain accurate nationwide cancer data of diagnosed cases in all hospitals of the 47 prefectures in Japan, thereby facilitating the collection of detailed information on duodenal cancer.[14] The large amount of data collected in 2016 were thoroughly filtered by the government and made available to researchers in 2019. In this study, we aimed to elucidate the incidence and clinical features of duodenal cancer using annual data from the Japanese population. In addition, we reviewed previous studies on the epidemiology of duodenal cancers to serve as references for this study. Herein, we report the first analysis of data on duodenal cancer from a national cancer registry.

Methods

Data collection. The analysis of this national data was approved by the Japanese Ministry of Health, Labour and Welfare, and the study protocol was accepted by the ethics committee of our institution. The Japanese national cancer registry classifies tumors according to the *International Classification of Disease for Oncology*, third edition. For the present study, we defined duodenal cancer using *International Classification of Disease for Oncology*, third edition, with topography code C17.0 and morphology codes 8000–8576/behavior recode 2 or 3.[15] Therefore, malignant neoplasm of the Vater's ampulla (topography code: C24.1), malignant lymphoma (morphology code 9590–9600), and stromal tumors like gastrointestinal stromal tumor (morphology code 8930–8990) were eliminated during data retrieval. We also excluded neuroendocrine tumor (morphology codes 8240, 8246, and 8249). Eventually, we included patients with newly diagnosed primary non-ampullary duodenal cancer from January 1, 2016, to December 31, 2016. For each patient, we retrieved data regarding the following factors: sex, age, detection mode (screening, incidental, symptomatic, or autopsy/unspecified), tumor stage (localized, regional lymph node metastasis, invasion to adjacent organ, distant metastasis, or unspecified), and treatment method (surgery, endoscopic resection, radiation therapy, chemotherapy, or unspecified). Regarding the detection mode, screening detection included cases detected by cancer screening for gastric cancer or medical checkup; and incidental detection was defined when diagnosis occurred during follow up or surveillance for other diseases. Advanced cancer was defined when metastasis or local invasion to adjacent organs was observed.

Literature screening and review. This literature review was a framework registered in an international database of prospectively registered systematic reviews (PROSPERO registration number: CRD42020142009). For the first screening, two independent investigators searched the literature using search terms such as "duodenal neoplasms/epidemiology" or "intestinal neoplasms/epidemiology" in PubMed, Cochrane Library, and Japan Medical Abstracts Society up to March 2019. The inclusion criteria of the second screening were as follows: (i) description of the incidence of duodenal cancer for the general population, (ii) description of survey duration and location, and (iii) description of the methodology used to calculate the incidence. We excluded studies involving patients with conditions associated with a high risk of duodenal cancer, such as familial adenomatous polyposis (FAP), Lynch syndrome, or *MUTYH*-associated polyposis.

Statistical analysis. We calculated the incidence of duodenal cancer in the population as a crude number of patients with duodenal cancer divided by the total number of individuals in the Japanese population in 2016. Categorical data were analyzed using χ^2 tests and were expressed as frequencies with percentages, whereas continuous data were analyzed using Student's t tests and were expressed as means with standard deviations. After excluding patients with incomplete data, we performed multivariate analyses using logistic regression models to identify risk factors associated with advanced cancer. We included all preoperative factors such as sex, age, and detection mode in the multivariate analyses. We reported the odds ratio (OR) with 95% confidence interval (CI) for each risk factor evaluated. Two-sided P values were calculated, and values <0.05 were considered to indicate statistical significance. We performed statistical analyses using JMP Version 11.2.1 (SAS Institute Inc., Cary, NC, USA).

Results

Registry data. There were 3005 patients with duodenal cancer in this study, of which, 1905 (63.4%) were men and 1100 (36.6%) were women. The total mean age was 68.7 ± 12.5 years (Table 1). The incidence of duodenal cancer was 23.7 per 1 000 000 person-years. The incidence increased among persons of 60 years of age, and 60–80 years was the common age range of onset in both sexes (Fig. 1). The main detection mode of tumors was incidental detection (n = 1241; 41.3%), followed by other modes including being symptomatic (n = 1164; 38.7%) and routine screening tests (n = 414; 13.8%). At the time of detection, the tumor stages in patients were localized (n = 1694; 56.4%), regional lymph node metastasis (n = 168; 5.6%), invasion to adjacent organ (n = 259; 8.6%), and distant metastasis (n = 475; 15.8%). Distributions of the different treatment modalities were as follows: open surgery (n = 807; 26.9%), laparoscopic surgery (n = 179; 6.0%), endoscopic resection (n = 843; 28.1%), radiation (n = 16; 0.5%), and and/or chemotherapy (n = 421; 14%). Furthermore, 1739 (57.9%) patients underwent surgical or endoscopic resection.

Table 2 presents the comparison of characteristics between patients with localized and advanced duodenal cancer. There was no

Table 1 Characteristics of patients diagnosed with duodenal adenocarcinoma by primary tumor localization (n = 3005)

Sex, *n* (%)	
Male	1905 (63.4)
Female	1100 (36.6)
Age, mean ± SD	68.7 ± 12.5
Detection, *n* (%)	
Screening	414 (13.8)
Incidental	1241 (41.3)
Symptomatic	1164 (38.7)
Autopsy/unknown	186 (6.2)
Stage, *n* (%)	
In situ	182 (6.1)
Localized	1512 (50.3)
Regional LNM	168 (5.6)
SI	259 (8.6)
Distant metastasis	475 (15.8)
Unknown	409 (13.6)
Treatment[†], *n* (%)	
Open surgery	807 (26.9)
Laparoscopic surgery	179 (6.0)
Endoscopic resection	843 (28.1)
Chemotherapy	421 (14.0)
Radiation therapy	16 (0.5)

[†]Treatment strategy was duplicated.

LNM, lymph node metastasis; SD, standard deviation; SI, tumor invades adjacent structures.

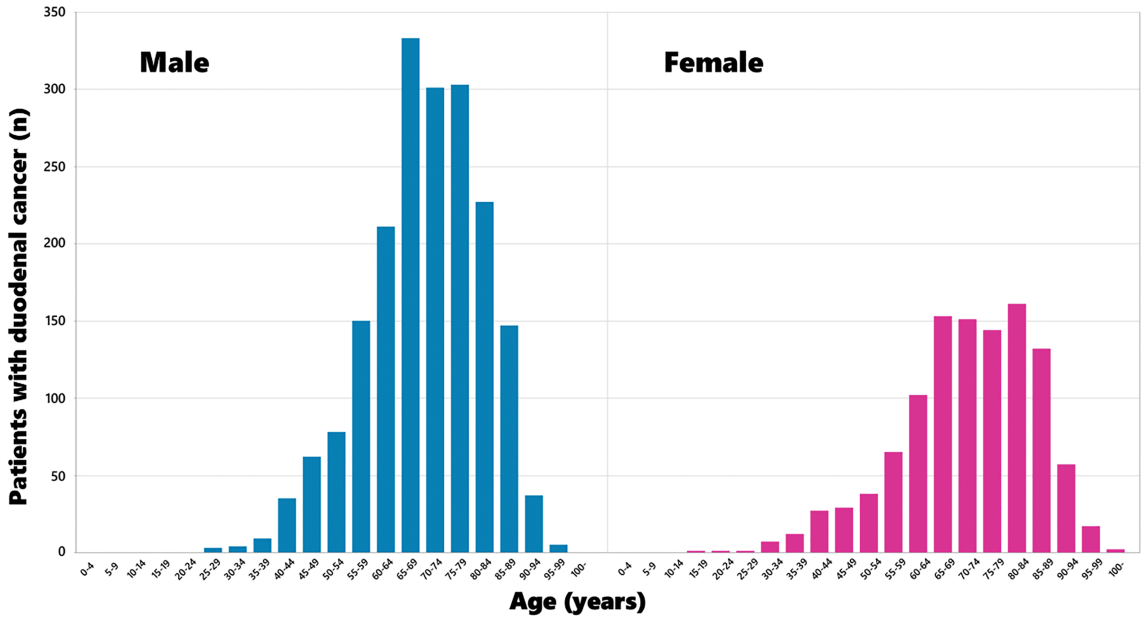

FIGURE 1 Distribution of age (at diagnosis) of patients with duodenal cancer in the Japanese national cancer registry. The incidence increased among individuals aged 60 years, and 60–80 years was the most common age range of onset in both sexes.

significant difference in sex distribution between the two groups. Patients with localized cancer were significantly younger than those with advanced cancer (66.9 ± 12.3 years *vs* 69.9 ± 12.0 years, $P < 0.0001$). Localized cancer was detected significantly more frequently by screening examination (20.8% *vs* 4.6%, $P < 0.0001$) or by chance (50.7% *vs* 27.9%, $P < 0.0001$) than advanced cancer. The detection mode was significantly different between patients with localized *versus* advanced duodenal cancer ($P < 0.0001$); most patients with advanced cancer were detected by a precise examination for symptoms (local 26.0% *vs* advanced 65.4%). The frequencies of the various treatment modalities also significantly differed between the groups ($P < 0.0001$ for all). In the localized cancer group, endoscopic resection was the most frequently applied treatment modality (48.0%), whereas in the advanced cancer group, open surgery and chemotherapy were the major treatment options (39.3% and 41.5%, respectively).

Risk factors for advanced cancer. Multivariate analyses identified age ≥80 years (OR, 1.489; 95% CI, 1.113–1.992), incidental detection (OR, 2.325; 95% CI, 1.623–3.331), and precise examination for symptomatic patients (OR, 10.561; 95% CI, 7.416–15.042) as significant independent risk factors for advanced cancer (Table 3).

Table 2 Comparison of clinical characteristics between patients with localized and advanced cancer

	Localized (n = 1694)	Advanced(n = 902)	P value
Sex, n (%)			0.31
Male	1112 (65.6)	574 (63.6)	
Female	582 (34.4)	328 (36.4)	
Age, mean ± SD	66.9 ± 12.3	69.9 ± 12.0	<0.0001
Detection, n (%)			<0.0001
Screening	352 (20.8)	41 (4.6)	
Incidental	859 (50.7)	252 (27.9)	
Symptomatic	440 (26.0)	440 (65.4)	
Unknown	43 (2.5)	19 (2.1)	
Treatment[†], n (%)			
Endoscopic resection	813 (48.0)	13 (1.4)	<0.0001
Open surgery	447 (26.4)	354 (39.3)	<0.0001
Laparoscopic surgery	158 (9.3)	16 (1.8)	<0.0001
Chemotherapy	30 (1.8)	374 (41.5)	<0.0001
Radiation therapy	1 (0.1)	14 (1.6)	<0.0001

[†]Treatment strategy was duplicated.
SD, standard deviation.

Table 3 Clinical factors associated with advanced duodenal cancer

	OR	Lower 95% CI	Upper 95% CI	*P* value
Sex				
Male	Reference	—	—	—
Female	1.019	0.845	1.228	0.846
Age (years)				
≤ 59	Reference	—	—	—
60–69	1.183	0.891	1.572	0.246
70–79	1.080	0.816	1.430	0.590
≥ 80	1.489	1.113	1.992	0.007
Detection				
Screening	Reference	—	—	—
Incidental	2.325	1.623	3.331	<0.0001
Symptomatic	10.561	7.416	15.042	<0.0001

CI, confidence interval; OR, odds ratio.

Literature review. At the first screening, 281 articles were detected and reviewed, whereas after the second screening, six articles were identified (Table 4). The incidence of duodenal adenocarcinoma was reported as 2.9–3.7 per 1 000 000 person-years in the United States and 2.9–4.3 in European countries.

Discussion

To the best of our knowledge, this is the first study in Asia to report details of duodenal cancer based on the data from a national cancer registry database. Large-scale data from all hospitals in Japan were collected according to the law and are, therefore, reliable. Our study revealed that the incidence of duodenal cancer was 23.7 per 1 000 000 person-years, and approximately 65% of patients had localized cancer. Endoscopic resection was mainly applied for localized cancer, whereas open surgery and chemotherapy were mainly adopted for advanced cancer. More than 80% of patients with localized cancer underwent endoscopic or surgical resection, whereas only 40% of those with advanced cancer underwent surgical treatment. Furthermore, we identified that older age (≥80 years), incidental detection, and symptomatic detection were risk factors for advanced cancer.

Our study revealed that the incidence of duodenal cancer in Japan is remarkably high. First, widespread esophagogastroduodenoscopy (EGD) such as screening for gastric cancer, health check, and surveillance for other diseases such as chronic gastritis with detailed observation of the duodenal area might explain the high incidence rate in Japan. Furthermore, the high accessibility and low cost of EGD in Japan might have contributed to the high incidence of incidentally detected duodenal cancer during follow up or surveillance EGD for other diseases. Second, Japan has been facing an aging society as seen in other developed countries. According to reports from Western countries, the incidence of duodenal cancer has been increasing.[5,6,13,17] The incidence increased from 1.5 to 4.1 per 1 000 000 person-years in the United States from 1973 to 2005, from 2.7 to 4.3 in the Netherlands from 1999 to 2013, and from 0.7 to 4.2 in Sweden from 2005 to 2009. Although racial differences should be considered, Qubaiah *et al*.[5] reported that Asians do not have a high risk of developing small intestinal adenocarcinoma. We reported an annual incidence without age standardization because we did not study the chronological trend in Japan. To compare the incidence precisely, age standardization is required. However, previous studies adopted country's own age standardization, resulting in difficulty of a direct comparison. We additionally reconfirmed the incidence of duodenal cancer in this study by adjusting population of the United States in 2000, revealing still high incidence as 13.3 per 1 000 000 person-years (Table S1). Moreover, crude incidence in Denmark was 2.9 per 1 000 000 person-years.[7] Third, the pathological diagnostic system for gastrointestinal cancers has not been unified between Japan and the Western countries. Japanese pathologists diagnose lesions as cancer on the basis of the degree of structural and cytological abnormality of tumor glands, while pathologists in the West make a diagnosis of cancer when there is histological evidence of invasion into the lamina propria or beyond the submucosa.[18] Although the carcinoma *in situ* of this study was only 6.1%, the pathological difference might affect the incidence. Further studies from Asian countries are required to clarify the trend and the incidence among ethnic groups.

Although there was little difference in the incidence between men and women in the European population,[13] our results showed that duodenal cancer occurred 1.7 times more commonly in men than in women. Across the age-group distribution of duodenal cancer, approximately 55% of cases occurred in individuals aged 60–70 years,[6] a finding similar to our results. The incidence increased with age.[5,7]

Although only 10–22% of patients were diagnosed at the localized tumor stage in Western countries, more than 50% were diagnosed at this stage in Japan.[5,7] Moreover, approximately 48% of local duodenal cancers were treated by endoscopic

Table 4 Literature review for incidence of duodenal cancer

No.	Authors	Study design	Country	Study period	Age standardization	Incidence[†]
1	Haselkorn *et al.*[16]	Cross-sectional	United States	1973–2000	United States 2000	2.9[‡]
2	Schottenfeld *et al.*[17]	Cross-sectional	United States	1973–2005	United States 2000	3.0[‡]
3	Qubaiah *et al.*[5]	Cross-sectional	United States	1992–2006	United States 2000	3.7[‡]
4	Lu *et al.*[13]	Cross-sectional	Sweden	1960–2009	Sweden 2000	4.2[‡]
5	Bojesen *et al.*[7]	Cohort	Denmark	1994–2010	—	2.9[§]
6	Legue *et al.*[6]	Cross-sectional	Netherlands	1999–2013	European standardized population	4.3[‡]
7	Present study	Cross-sectional	Japan	2016	—	23.7[§]

[†]Per 1 000 000 person-years.
[‡]Age-standardized incidence.
[§]Crude incidence.

resection. Advanced duodenal cancer has a poor prognosis[7]; therefore, early detection is required. Favorable short-term and long-term outcomes of endoscopic treatment at early stages were reported in Japan.[19–24] Our study results indicated that conducting screenings in individuals aged <80 years would contribute to the early detection of this disease and an improvement in its prognosis. As duodenal cancer is relatively rare, endoscopic screening specifically for duodenal cancer should not be currently performed because of the limited capacity of some medical institutions and poor cost effectiveness. Previous studies reported that most duodenal cancers were detected in the first or second portion of the duodenum.[25,26] Therefore, as a routine, it would be reasonable to evaluate the duodenum in the second portion during screening or surveillance EGD.

Our study had some limitations. First, we included some FAP cases in our study population. However, the prevalence of FAP in the Japanese population is approximately 0.006%, and thus, its inclusion likely had limited effects on the study results.[27] Second, we did not mention trends because this is a 1-year report. We are conducting a further study to accumulate cases. Third, there might be differences in the use of technical terms between Japan and the Western countries, and we did not validate our data outside Japan. Consequently, consensus on diagnostic criteria for duodenal cancer is required and large-scale studies from other countries are needed to validate our data outside Japan.

In conclusion, our study elucidated the high incidence of duodenal cancer in Japan. Most cases were diagnosed at the localized tumor stage, resulting in a high rate of resection. Independent risk factors for advanced duodenal cancer were age ≥80 years and detection at a symptomatic stage. The results of our analyses improved our understanding of the current situation in Japan. This could potentially be extrapolated to the neighboring Asian countries until further large-scale studies are conducted in Asian populations to validate these findings.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Age-standardization based on the US 2000 population.