Table 1 – General characteristics of the included studies.

Reference	Study interval	Country	Design	Surgery	Group	No. of patients	M/F	Mean age (y)	Etiology of malignancy, n (%)	Level of evidence
Sugiyama *et al.* (2004)	NM	Japan	Retro	PPPD	AG	12	7/5	62 ± 2	10 (83.3)	2b
					RG	18	10/8	60 ± 3	15 (83.3)	
Kurosaki *et al.* (2005)	1996–2002	Japan	Retro	PPPD	AG	25	13/12	65	25 (100)	4
					RG	19	10/9	61	17 (89.5)	
Hartel *et al.* (2005)	1996–2003	Germany	Pro	PPPD	AG	100	41/59	61 (53–71)	70 (70)	2b
					RG	100	46/54	65 (53–74)	75 (75)	
Tani *et al.* (2006)	2002–2004	Japan	RCT	PPPD	AG	20	11/9	63.1 ± 9.21	16 (80)	1b
					RG	20	10/10	66.7 ± 12.2	16 (80)	
Murakami *et al.* (2008)	1994–2006	Japan	Retro	PPPD	AG	78	46/32	67 ± 11	49 (62.8)	2b
					RG	54	36/18	64 ± 12	39 (72.2)	
Nikfarjam *et al.* (2009)	2002–2008	USA	Retro	CPD	AG	36	20/16	67 (21–88)	26 (72.2)	2b
					RG	36	20/16	67 (46–84)	15 (41.7)	
Gangavatiker *et al.* (2011)	2006–2008	India	RCT	CPD/PPPD	AG	32	23/9	52.8 ± 11.6	27 (84.4)	1b
					RG	36	26/10	50.8 ± 10.6	32 (88.9)	
Kurahara *et al.* (2011)	2007–2010	Japan	RCT	SSPPD	AG	24	16/8	67.6 ± 11.6	18 (75)	1b
					RG	22	16/6	62.3 ± 12.6	17 (77.3)	
Oida *et al.* (2012)	2000–2009	Japan	Retro	SSPPD	AG	14	10/4	65.7 ± 6.7	14 (100)	4
					RG	28	20/8	65.8 ± 5.4	28 (100)	
Tamandl *et al.* (2014)	2007–2009	Austria	RCT	PPPD	AG	36	17/19	67.1 (55.7–75.3)	25 (69.4)	1b
					RG	28	12/16	65.4 (55.6–70.6)	19 (67.9)	
Cordesmeyer *et al.* (2014)	2004–2011	Germany	Retro	PPPD	AG	28	15/13	63.5 (34–83)	NM	2b
					RG	45	22/23	70 (29–82)	NM	
Imamura *et al.* (2014)	2005–2011	Japan	RCT	PPPD	AG	58	36/22	70 (36–86)	46 (79.3)	1b
					RG	58	32/26	69 (46–86)	49 (84.5)	
Eshuis *et al.* (2014)	2009–2011	The Netherlands	RCT	PPPD/CPD	AG	121	83/38	65.4 ± 9.0	108 (90)	1b
					RG	125	68/57	65.2 ± 10.3	119 (95.2)	
Sahora *et al.* (2014)	2000–2012	USA	Retro	CPD	AG	400	209/191	64 (21–91)	280 (70)	2b
					RG	400	191/209	67 (26–92)	281 (70.2)	

Retro = retrospective study; Pro = prospective study; PPPD = pylorus-preserving pancreatoduodenectomy; CPD = classic pancreatoduodenectomy; SSPPD = subtotal stomach-preserving pancreatoduodenectomy; NM = not mentioned.

3.3.7. *Mortality*

This analysis was conducted with 13 studies. There was no heterogeneity among the included studies (chi-square = 2.48, df = 5 [P = 0.78]; I^2 = 0%). In a fixed-effect model, there was no significant difference in mortality between the AG and the RG (OR = 0.93 [0.42–2.03], Z = 0.19, P = 0.85; Fig. 3F).

4. Discussion

In the present study, data from RCTs and clinical observational studies were compiled as extensively as possible based on the selection criteria to analyze the relationship between gastro/duodenojejunal reconstruction route and DGE. Based on this meta-analysis including all 14 studies, it was found that antecolic reconstruction of G/DJ after PD is associated with a decreased incidence of DGE, reduced postoperative duration of hospital stay, and shortened duration until starting solid foods, but not with increased incidence of postoperative complications such as pancreatic fistula, intraperitoneal fluid retention and/or abscess, and biliary fistula, or with increased mortality. However, in subgroup analyses of six RCTs and of seven studies that were in accordance with the ISGPS definition, it was proven in each analysis that it is difficult to decrease the incidence of DGE after PD using antecolic reconstruction.

Since the first description of post-PD DGE by Warshaw *et al.* in 1985 [36], many studies of the cause of DGE have been reported. Although the cause of DGE has yet to be elucidated, it is considered that various factors induce DGE. Some of these factors include decreased circulating motilin levels because of resection of the duodenum and proximal jejunum [37], nerve damage resulting from dissection of lymph nodes along the common hepatic artery [38], ischemia at the pyloric antrum region or anastomosis site caused by right gastric artery dissection [39], and complications at other abdominal areas, such as pancreatic fistula, intraperitoneal abscess, and local inflammation [40]. Additionally, various techniques in reconstruction surgery have been devised to reduce the incidence of DGE after PD. Of such techniques, the antecolic reconstruction of gastro/duodenojejunostomy is one of the most commonly recommended procedures from the perspective of reducing the incidence of DGE [6,9,10,15,17,33,35]. The advantages of this technique are that it involves a region that is not in close proximity to areas that have risks of anastomotic leaks, such as the pancreaticojejunostomy site or choledochojejunostomy site, that the mechanical twisting and bending of the reconstructed digestive tract can be kept to a minimum [21], and

Table 2 – Surgical technique, definition of delayed gastric emptying and postoperative management.

Reference	Group	Reconstruction		Definition of DGE	SSA	Antacid	PA	DGE, *n* (%)
Sugiyama *et al.* (2004)	AG	E-T-S PJ	E-T-S DJ	NGT ≥ POD 10	NM	H2 blocker	No	1 (8.3)
	RG							13 (72.2)
Kurosaki *et al.* (2005)	AG	E-T-S PJ	E-T-S DJ	1. NGT ≥ POD 10	NM	NM	NM	2 (8)
	RG	E-T-S PJ or PG	E-T-E DJ	2. Reinsertion of NGT				14 (73.7)
Hartel *et al.* (2005)	AG	E-T-S PJ	E-T-S DJ	1. NGT ≥ POD 10	Yes	PPI	Yes	5 (5)
	RG			2. Inability to tolerate a solid diet ≤ POD 10				24 (24)
				3. Vomiting ≥3 consecutive days after POD 5, etc.				
Tani *et al.* (2006)	AG	E-T-S PJ	E-T-S DJ	1. NGT ≥ POD 10	No	H2 blocker	No	1 (5)
	RG			2. Reinsertion of NGT				10 (50)
				3. Failure of unlimited oral intake by POD 14				
Murakami *et al.* (2008)	AG	E-T-S PG	E-T-S DJ	1. NGT ≥ POD 10	No	H2 blocker	NM	8 (10.3)
	RG		E-T-E DJ	2. Inability to tolerate a solid diet < POD 14				44 (81.5)
Nikfarjam *et al.* (2009)	AG	E-T-S PJ	E-T-S GJ	ISGPS definition	NM	PPI	Yes	5 (13.9)
	RG							14 (38.9)
Gangavatiker *et al.* (2011)	AG	E-T-S PJ	E-T-S DJ or GJ	ISGPS definition	Yes	PPI	No	11 (34.4)
	RG							10 (27.8)
Kurahara *et al.* (2011)	AG	E-T-S PG	E-T-S GJ	ISGPS definition	No	H2 blocker	No	5 (20.8)
	RG							11 (50)
Oida *et al.* (2012)	AG	E-T-S PG	E-T-S GJ	ISGPS definition	NM	NM	NM	14 (100)
	RG							28 (100)
Tamandl *et al.* (2014)	AG	E-T-S PJ	E-T-S DJ	1. NGT ≥ POD 10	No	NM	No	6 (17.6)
	RG			2. Reinsertion of NGT				6 (23.1)
				3. Failure to progress with the diet, etc.				
Cordesmeyer *et al.* (2014)	AG	E-T-S PJ	E-T-S DJ	ISGPS definition	No	PPI	No	1 (4.5)
	RG							10 (27)
Imamura *et al.* (2014)	AG	E-T-S PJ	E-T-S DJ	ISGPS definition	No	PPI	No	7 (12.1)
	RG							12 (20.7)
Eshuis *et al.* (2014)	AG	E-T-S PJ	E-T-S DJ or GJ	ISGPS definition	Selected	NM	No	74 (61.2)
	RG							75 (60)
Sahora *et al.* (2014)	AG	E-T-S PJ	E-T-S GJ	ISGPS definition	NM	NM	No	59 (14.8)
	RG							84 (21)

E-T-S = end to side; E-T-E = end to end; PJ = pancreaticojejunostomy; PG = pancreaticogastrostomy; DJ = duodenojejunostomy; GJ = gastrojejunostomy; ISGPS = International Study Group of Pancreatic Surgery; SSA = somatostatin analogs; PPI = proton pump inhibitors; PA = prokinetic agents; NM = not mentioned.

that the elimination of gastric content is promoted with gravity [20].

However, according to recently reported RCTs and retrospective studies that compared antecolic and retrocolic reconstructions of G/DJ after PD, antecolic reconstruction did not lead to a reduction in DGE incidence [18–21,32], resulting in a controversy. Indeed, based on the Forest plot of the present meta-analysis of all 14 studies, it is evident that there are more studies in recent years in which the odds ratio of DGE incidence intersects with the line at 1. In other words, although the overall result of individual studies has demonstrated the efficacy of antecolic reconstruction, recent studies have shown tendencies for lower efficacy of antecolic reconstruction. This observation was validated by the present study's subgroup analyses involving six RCTs and seven recent studies that were in accordance with the ISGPS definition.

The reasons why recent reports did not prove the efficacy of the antecolic route to treat DGE need to be considered. Eshuis *et al.* (the largest RCT, $n = 245$) presented the following reconstruction method as a difference from the previously reported retrocolic reconstruction method. After opening a separate hole on the left side of the transverse mesocolon, the gastro/duodenal stump was passed through the caudal side of the mesocolon, and the stomach was fixed to the transverse mesocolon. Because the site of G/DJ was positioned at a section at a distance from important anastomosis sites, such as the pancreaticojejunostomy site or choledochojejunostomy site, the effects of infection and inflammation were avoided. Furthermore, the twisting and bending of the reconstructed gastrointestinal tract can be hindered because of fixation. They considered the above observations to be the likely causes that led to the absence of differences between antecolic and retrocolic reconstructions in the incidence of DGE. Imamura *et al.* (medium-scale RCT, $n = 116$) also reported that the retrocolic reconstruction they perform results in DGE at a similar frequency as previously reported antecolic reconstructions, demonstrating that there were no significant differences between antecolic and retrocolic reconstructions. Moreover, in addition to a retrocolic procedure similar to the technique

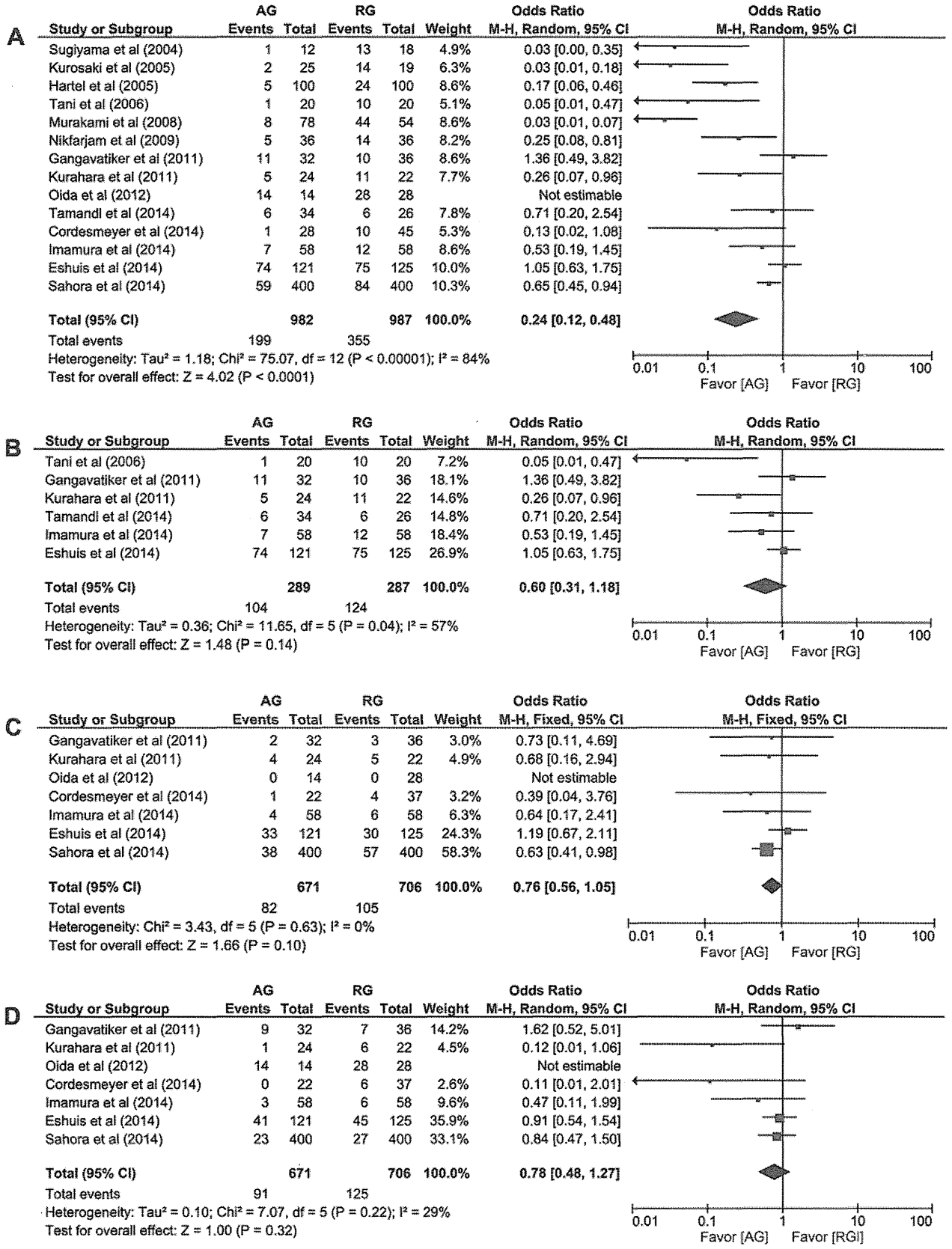

Fig. 2 – Forest plots displaying the results of the meta-analysis on DGE: (A) all studies, (B) randomized controlled trials (RCTs), (C) Grade A of the ISGPS definition, and (D) Grade B and C of the ISGPS definition. Pooled ORs with 95% CIs were calculated using Mantel–Haenszel (M–H) fixed-effect or random-effects models. (Color version of figure is available online.)

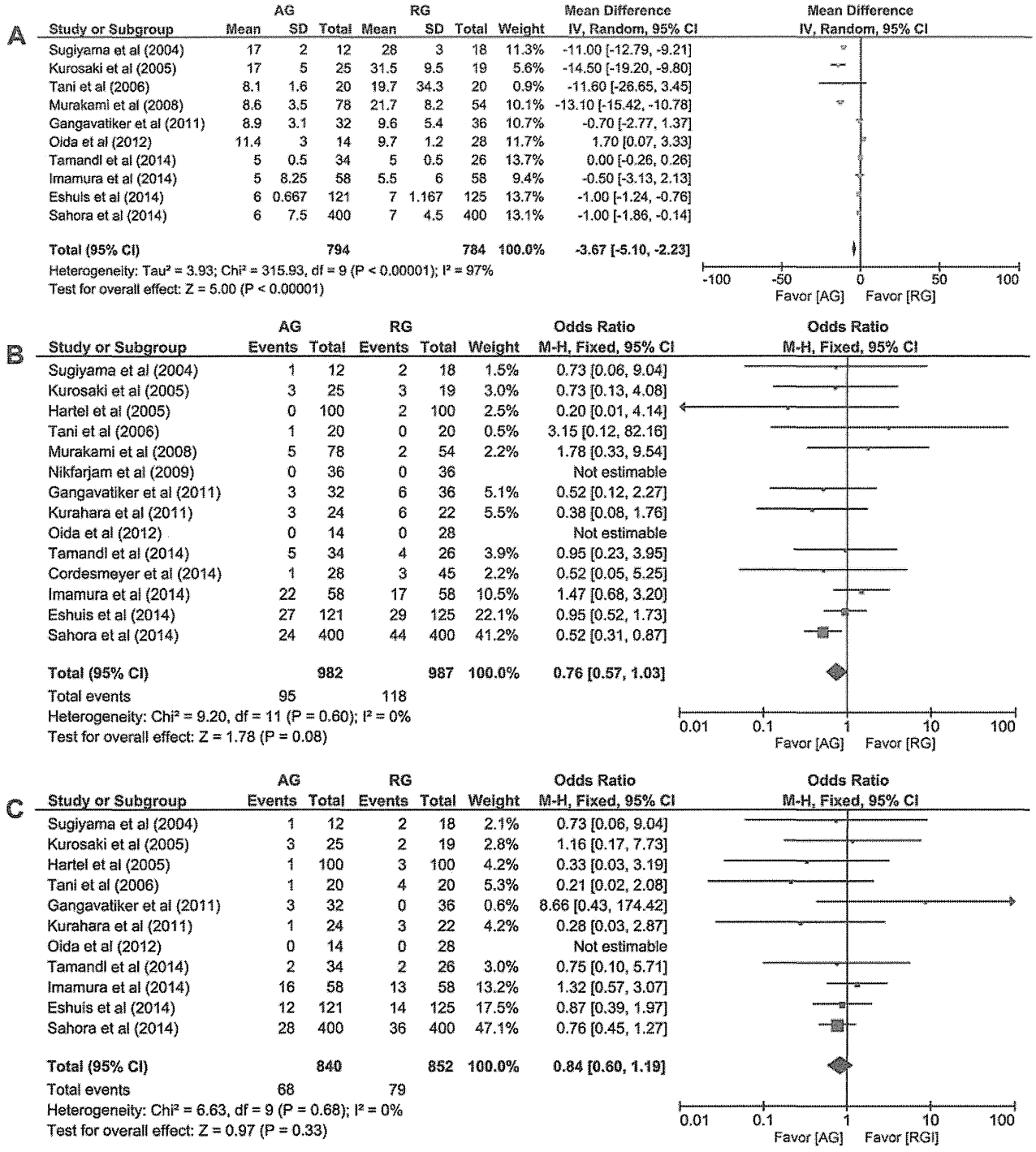

Fig. 3 – Forest plots displaying the results of the meta-analysis on postoperative outcomes and complications: (A) days to start solid foods, (B) pancreatic fistula, (C) intra-abdominal fluid collection/abscess, (D) biliary fistula, (E) length of postoperative hospital stay, and (F) mortality. Pooled ORs with 95% CIs were calculated using Mantel–Haenszel (M–H) fixed-effect or inverse variance (IV) random-effects models. SD = standard deviation. (Color version of figure is available online).

described by Eshuis *et al.*, they arranged the reconstructed stomach vertically and linearly and suggested that this may have contributed to the elimination of stomach content through gravity.

In addition, reports before 2009 conducted DGE evaluations using their own specific definitions. Thus, results may have been different from recent studies that were conducted in accordance with the ISGPS definition. ISGPS classifies DGE into Grade A, B, or C based on the clinical impact [23]. From the subgroup analysis conducted in the seven studies that were in accordance with this ISGPS definition, the efficacy of antecolic reconstruction was not demonstrated in any of these three grades of DGE. (Grade A is clinically mild, whereas grades B and C have moderate or greater severity of DGE).

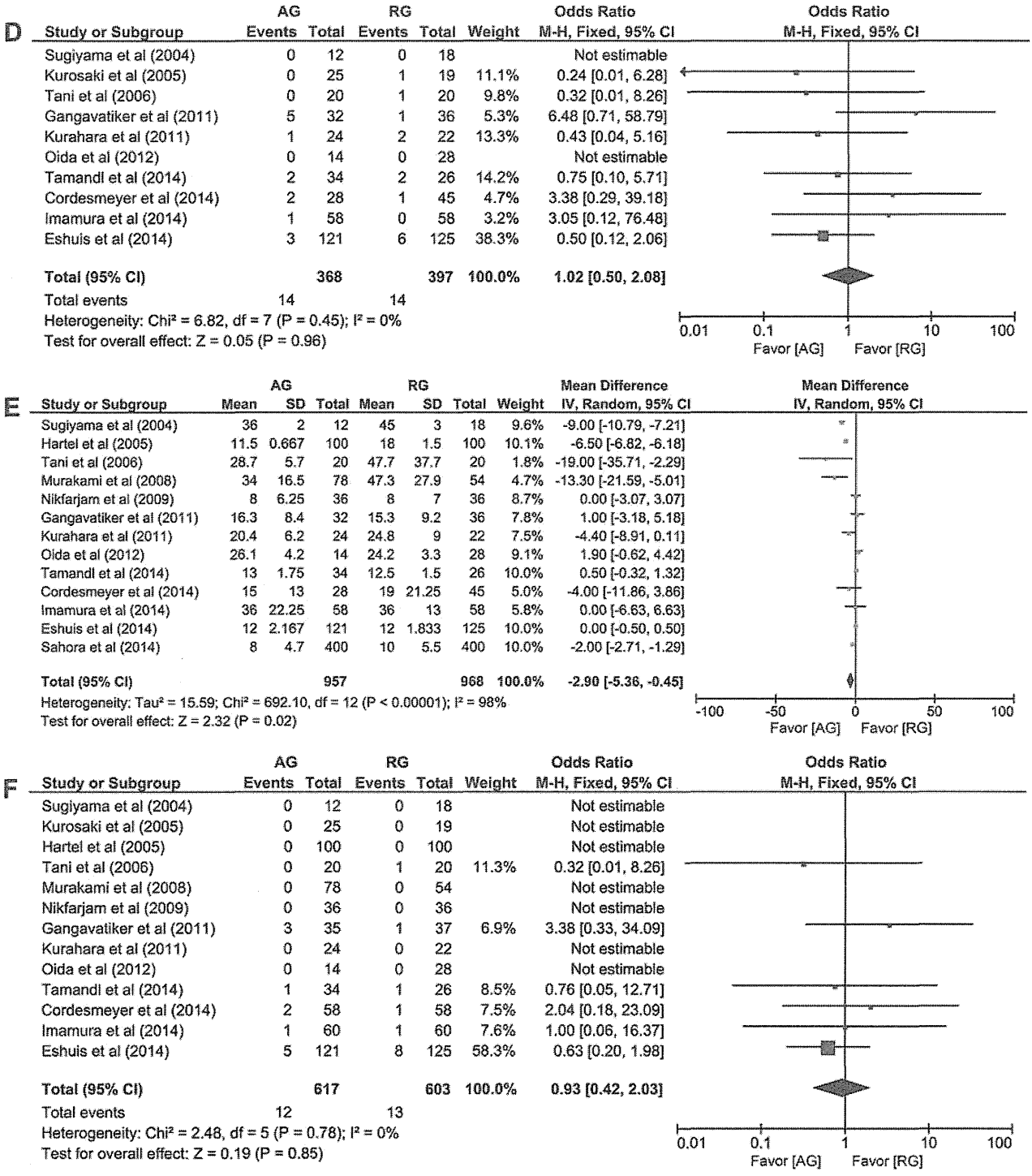

Fig. 3 – (*continued*).

There are several limitations with respect to the final results of this meta-analysis. The first is that both RCTs and non-RCTs were included in the analysis. The second is that substantial heterogeneity was observed in the analysis of DGE and the day of starting solid foods. Several factors may have contributed to this observation, such as the differences in the definition of DGE used in each study, the surgical procedures (Billroth I or Billroth II for gastro/duodenojejunal reconstruction, pancreaticojejunostomy or pancreaticogastrostomy for pancreatic-digestive tract reconstruction), and the use of postoperative medications (somatostatin analogs, antacids, and prokinetic agents). To reduce the heterogeneity, subgroup analyses, focusing on only RCTs or only ISGPS-defined studies, were conducted. The results, however, did not demonstrate associations between reconstruction route and DGE.

To reach an evidence-based consensus on the effect of antecolic *versus* retrocolic reconstruction for G/DJ on DGE after

PD, much larger and well-structured RCTs with a defined technique and postoperative management would be needed, while using the ISGPS definition of DGE.

In conclusion, the present meta-analysis demonstrated that the antecolic reconstruction route in G/DJ after PD may be associated with a reduction in postoperative hospital stay and early resumption of oral consumption, but it may not decrease the incidence of DGE.

Acknowledgments

Authors' contributions: M.I., Y.K., and K.H. participated in study conception and design. M.I., T.K., T.I., and T.N. did the acquisition of data. M.I. and Y.K. performed the analysis and interpretation of data. M.I. and Y.K. drafted the article. T.M. and K.H. performed the critical revision of the article.

Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in the article.

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J Gastroenterol (2015) 50:58–64
DOI 10.1007/s00535-014-0934-2

The Japanese Society of Gastroenterology

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Epidemiological trends of pancreatic and gastrointestinal neuroendocrine tumors in Japan: a nationwide survey analysis

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Received: 29 July 2013 / Accepted: 10 January 2014 / Published online: 6 February 2014

Abstract
Background Although neuroendocrine tumors (NETs) are rare, the number of patients with NET is increasing. However, in Japan, there have been no epidemiological studies on NET since 2005; thus, the prevalence of NET remains unknown.
Methods We reported the epidemiology of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) [pancreatic neuroendocrine tumors (PNETs) and gastrointestinal neuroendocrine tumors (GI-NETs)] in Japan in 2005. Here, we conducted the second nationwide survey on patients with GEP-NETs who received treatment in 2010.
Results A total of 3,379 patients received treatment for PNETs in 2010, representing a 1.2-fold increase in the number of patients from 2005 to 2010. The prevalence was estimated to be 2.69/100,000, with an annual onset incidence of 1.27/100,000 in 2010. Non-functioning tumor (NF)-PNETs comprised 65.5 % of cases followed by insulinoma (20.9 %) and gastrinoma (8.2 %). Interestingly, the number of patients with NF-PNETs increased ~1.8 fold since 2005. A total of 19.9 % of patients exhibited distant metastasis at initial diagnosis; 4.3 % had complications with multiple endocrine neoplasia type 1 (MEN-1), and only 4.0 % had NF-PNETs associated with MEN-1. Meanwhile, an estimated 8,088 patients received treatment for GI-NETs, representing a ~1.8-fold increase since 2005. The prevalence was estimated to be 6.42/100,000, with an annual onset incidence of 3.51/100,000. The locations of GI-NETs varied: foregut, 26.1 %; midgut, 3.6 %; and hindgut, 70.3 %. Distant metastasis and complications with MEN-1 were observed in 6.0 and 0.42 % at initial diagnosis, respectively. The frequency of carcinoid syndrome in patients with GI-NETs was 3.2 %.
Conclusion We clarified the epidemiological changes in GEP-NETs from 2005 to 2010 in Japan.

Keywords Neuroendocrine tumor · Pancreatic neuroendocrine tumor · Gastrointestinal neuroendocrine tumor · Nation-wide survey · Epidemiology

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Introduction

Neuroendocrine tumors (NETs) are generally considered rare tumors that progress slowly [1]. However, according to the surveillance, epidemiology, and end results (SEER) study, a US epidemiological database, the number of patients has been increasing; the incidence rate of the disease increased fivefold from 1.09 per 100,000 people in 1973 to 5.25 per 100,000 people in 2004 [2]. Although the reasons for this increase are unclear, the recognition of the disease and improved diagnostic technology may be partially responsible. Thus, continued accumulation and examination of data regarding the trend of the actual number of patients is necessary [3, 4].

However, in Japan, the prevalence of gastroenteropancreatic NETs (GEP-NETs) [pancreatic endocrine tumors (PNETs) and gastrointestinal neuroendocrine tumors (GI-NETs)] is unclear. Consequently, a nationwide epidemiological survey of patients with GEP-NET who received treatment from January 1 to December 31, 2005 was conducted in [5]; thus, the difference in the prevalence of the disease between Japan and Western nations gradually became clear. The large differences in GEP-NETs between Japan and Western nations are primarily due to differences in the presence of multiple endocrine neoplasia type 1 (MEN-1) in NF-PETs as well as the location, symptomatic status, and prevalence of malignancy in GI-NETs [5]. The present study reports the second nationwide survey on patients with GEP-NETs who received treatment in 2010. Furthermore, the epidemiological changes in these patients from 2005 to 2010 were examined.

Methods

We conducted the second nationwide survey to examine the epidemiology of GEP-NETs in Japan. The subjects were patients with GEP-NETs including PNETs and GI-NETs who received treatment from January 1 to December 31, 2010. Subjects were collected using a nationwide stratified random sampling method similar to that used in the first survey [5]. In brief, the departments of gastroenterology, gastroenterological surgery, endocrinology, and metabolic medicine of each hospital were listed, and stratified random sampling was used to select departments for the survey. The sampling rates for the stratum of general hospitals with <100, 100–199, 200–299, 300–399, 400–499, and ≥500 beds and university hospitals were 5, 10, 20, 40, 80, 100, and 100 %, respectively. To increase the efficiency of this survey, we added some relevant departments in which many patients with GEP-NETs were expected to be treated; they were considered a special stratum and were all selected. A questionnaire was directly mailed to the heads of the 6,339 randomly selected departments at the abovementioned sampling rates. Returned questionnaires providing information about 3,366 patients including 1,273 patients with PNETs and 2,093 with GI-NETs were collected. A response rate was 20.2 %. The diagnosis of GEP-NETs was classified according to the WHO 2010 criteria [6]. However, mixed adenoneuroendocrine carcinoma (MANEC) and hyperplastic and preneoplastic lesions were excluded. Regarding PNETs, patients with clinical symptoms and elevated plasma hormone levels were diagnosed as having a functioning PNET. On the other hand, patients without clinical symptoms and with no elevation of plasma hormone levels were diagnosed as having a nonfunctioning tumor (NF-PNET) regardless of whether the hormone production was evaluated by immunohistochemistry or mRNA detection in the tumor tissue.

Results

Epidemiology of PNETs in Japan

Epidemiology (Table 1)

The data collected from the present survey showed the estimated total number of patients treated for PNETs in the year 2010 was 3,379 [95 % confidence interval (CI) 3,173–3,580] and the overall prevalence was 2.69 per 100,000 people (95 % CI 2.29–3.08). This represents an approximately 1.2-fold increase since 2005. The total number of patients treated for functioning tumors was estimated to be 1,105 (95 % CI 868–1,342), and the overall prevalence was 0.88 per 100,000 people (95 % CI 0.65–1.05). On the other hand, the total number of patients treated for non-functioning tumors was estimated to be 2,274 (95 % CI 1,759–2,789), and the overall prevalence was 1.81 per 100,000 people (95 % CI 1.51–2.11). There were more patients with functioning PNETs than NF-PNETs in 2005, while the opposite trend was observed in 2010. The incidence rates of PNETs, functioning tumors, and NF-PETs in 2010 were estimated to be 1.27 per 100,000 people (95 % CI 1.08–1.46), 0.41 per 100,000 people (95 % CI 0.32–0.48), and 0.87 per 100,000 people (95 % CI 0.72–1.01), respectively. The number of new-onset functioning PNETs in 2010 was similar to that in 2005; however, the number of new-onset NF-PNETs in 2010 was approximately 1.7-fold greater than that in 2005.

Distribution of PNETs in Japan in 2010 (Table 2)

NF-PNETs were the most common PNETs in Japan in 2010, comprising 65.5 % of all PNETs. Meanwhile, functioning tumors comprised 34.5 % of PNETs. The most

Table 1 The trends of epidemiology of pancreatic neuroendocrine tumors (PNETs) from 2005 to 2010 in Japan

	2005*	2010
Total number of patients treated for PNET	2,845 (95 % CI 2,455–3,507)	3,379 (95 % CI 3,173–3,580)
Functioning tumors	1,627 (95 % CI 1,404–2,005)	1,105 (95 % CI 868–1,342)
Non-functioning tumors	1,218 (95 % CI 1,053–1,453)	2,274 (95 % CI 1,759–2,789)
Overall prevalence of PNETs (per 100,000 population)	2.23 (95 % CI 1.93–2.76)	2.69 (95 % CI 2.29–3.08)
Functioning tumors	1.27 (95 % CI 1.10–1.57)	0.88 (95 % CI 0.65–1.05)
Non-functioning tumors	0.95 (95 % CI 0.82–1.17)	1.81 (95 % CI 1.51–2.11)
Incidence rate of PNETs (per 100,000 population)	1.01 (95 % CI 0.88–1.25)	1.27 (95 % CI 1.08–1.46)
Functioning tumors	0.5 (95 % CI 0.44–0.62)	0.41 (95 % CI 0.32–0.48)
Non-functioning tumors	0.51 (95 % CI 0.88–1.25)	0.87 (95 % CI 0.72–1.01)

*Data modified from reference [5]

95 % CI 95 % confidence interval

Table 2 Distribution of pancreatic neuroendocrine tumors (PNETs) in 2010

	Number of patients	Percentage (%)
Functioning PNETs	439/1,273	34.5
Insulinoma	266/1,273	20.9
Gastrinoma	104/1,273	8.2
Glucagonoma	42/1,273	3.2
VIPoma	8/1,273	0.6
Somatostatinoma	4/1,273	0.3
Others	17/1273	1.3
Non-functioning PNETs	834/1,273	65.5

Table 3 Percentages of neuroendocrine carcinoma (NEC) among pancreatic and gastrointestinal neuroendocrine tumors in 2010

	Number of patients	Percentage (%)
(a) Total PNETs	95/1,273	7.5
Functioning PNETs	14/439	3.2
Insulinoma	5/266	1.9
Gastrinoma	6/104	5.8
Glucagonoma	1/42	2.4
VIPoma	0/8	0
Somatostatinoma	0/4	0
Others	2/17	11.8
Non-functioning PNETs	81/834	9.7
(b) Total GI-NETs	130/2,093	6.2
Foregut	93/737	12.6
Midgut	7/77	9.1
Hindgut	30/1,279	2.3

PNETs pancreatic neuroendocrine tumors, *GI-NETs* gastrointestinal neuroendocrine tumors

frequent functioning PNETs were insulinoma (20.9 %) followed by gastrinoma (8.2 %). Glucagonoma, VIPoma, and somatostatinoma had low frequencies of 3.2, 0.6, and 0.3 %, respectively.

Histopathological distribution of PNETs in Japan in 2010 (Table 3a)

The histological survey was conducted according to the 2010 WHO classification. This survey comprised 2 parts: one was for NETs (G1/G2) and the other for neuroendocrine carcinoma (NEC; small-cell or large-cell type). The frequency of NECs among all PNETs was 7.5 %. The frequency of NECs among NF-PNETs was high at the rate of 9.7 % compared with that among functioning PNETs at the rate of 3.2 %.

Percentages of distant metastases and association of MEN-1 in PNETs (Table 4)

Among the patients with PNETs, 19.9 % exhibited distant metastases at initial diagnosis; the percentages among functioning PNETs and NF-PNETs were 16.9 % and 21.3 %, respectively. Among functioning PNETs, gastrinoma accounted for 30.2 %, whereas insulinoma accounted for 9.3 %. With regard to the grade of WHO calcification, the percentage of distant metastases in patients with NEC at initial diagnosis was high at the rate of 46.3 % compared with that in patients with NET G1/G2 at the rate of 12.9 %. Especially, NF-PNETs patients with NEC was the most prevalent at the rate of 51.9 %.

On the other hand, complications with MEN-1 accounted for 4.3 % of all PNETs (4.9 % of functioning PNETs and 4.0 % of NF-PNETs). The percentage of complications with MEN-1 among cases of gastrinoma was high (16.3 %) but low among cases of insulinoma (0.8 %).

Epidemiology of GI-NETs in Japan in 2010

Epidemiology (Table 5)

The present survey estimated a total of 8,088 people (95 % CI 5,669–10,507) were treated for GI-NETs in 2010. The

total numbers of patients treated for foregut, midgut, and hindgut tumors in this group were 2,107 (95 % CI 1,189–3,028), 290 (95 % CI 271–349), and 5,690 (95 % CI 3,583–7,797), respectively. There were approximately 1.8 times as many patients in 2010 as those in 2005. The overall prevalence of GI-NETs was 6.42 per 100,000 people (95 % CI 4.50–8.34). The overall prevalences of foregut, midgut, and hindgut tumors were 1.67 (95 % CI 0.94–2.40), 0.23 (95 % CI 0.18–0.28), and 4.52 per 100,000 people (95 % CI 3.17–5.87), respectively. The locations of GI-NETs varied: 26.1, 3.6, and 70.3 % were in the foregut, midgut, and hindgut, respectively. Similar to the survey results from 2005, the frequency of midgut NETs was very low in Japan relative to that in Western nations. Meanwhile, the incidence rate of GI-NETs in 2010 was estimated to be 3.51 per 100,000 people (95 % CI 2.50–4.53); the incidence rates of foregut, midgut, and hindgut tumors in this group were 1.20 (95 % CI 0.48–1.91), 0.15 (95 % CI 0.12–0.18), and 2.12 per 100,000 people (95 % CI 1.56–2.67), respectively. Although the incidence rates of foregut and hindgut tumors clearly increased since 2005, no change in the incidence rate of midgut tumors was observed.

Table 4 Percentages of distant metastases and associated MEN-1 in pancreatic neuroendocrine tumors (PNETs) in 2010

	Distant metastases (%)			Associated MEN-1 (%)
	Total	NET G1/G2	NEC	
Total PNETs	19.9	12.9	46.3	4.3
Functioning PNETs	16.9	17.2	14.3	4.9
Insulinoma	9.3	9.7	0	0.8
Gastrinoma	30.2	32.4	10.7	16.3
Glucagonoma	8.3	9.1	0	8.3
VIPoma	80.0	80.0	0	0
Somatostatinoma	100	100	0	0
Others	25.0	0	50	0
Non-functioning PNETs	21.3	12.9	51.9	4.0

MEN-1 multiple endocrine neoplasia type 1

Histopathological distribution of GI-NETs in Japan in 2010 (Table 3b)

The frequency of NEC among all GI-NETs was 6.2 %. NEC was most common among foregut NETs (12.6 %) followed by midgut NETs (9.1 %) and hindgut NETs (2.3 %).

Percentages of distant metastases and association between MEN-1 and frequency of carcinoid syndrome in GI-NETs (Table 6)

Among all patients with GI-NETs, distant metastases were observed at initial diagnosis in 6.0 %. Regarding location, midgut NETs were the most common (9.8 %) followed by foregut NETs (8.6 %) and hindgut NETs (3.5 %). With regard with the grade of WHO calcification, the percentage of distant metastases in patients with NEC at initial diagnosis was high at the rate of 32.3 % compared with that in patients with NET G1/G2 at the rate of 2.7 %. Especially, foregut NETs patients with NEC was the most prevalent at the rate of 40.9 %.

Meanwhile, complications with MEN-1 were observed in 0.7 % of all GI-NETs. Regarding location, they were observed in 0.7, 0, and 0.2 % of foregut, midgut, and

Table 5 The trends of epidemiology of gastrointestinal neuroendocrine tumors (GI-NETs) from 2005 to 2010 in Japan

	2005*	2010
Total number of patients treated for GI-NETs	4,406 (95 % CI 3,321–5,420)	8,088 (95 % CI 5,669–10,507)
Foregut	1,338 (95 % CI 1,009–1,640)	2,107 (95 % CI 1,189–3,028)
Midgut	423 (95 % CI 319–520)	290 (95 % CI 271–349)
Hindgut	2,645 (95 % CI 1,994–3,254)	5,690 (95 % CI 3,583–7,797)
Overall prevalence of GI-NETs (per 100,000 population)	3.45 (95 % CI 1.93–4.24)	6.42 (95 % CI 4.50–8.34)
Foregut	1.05 (95 % CI 0.59–1.28)	1.67 (95 % CI 0.94–2.40)
Midgut	0.33 (95 % CI 0.18–0.41)	0.23 (95 % CI 0.18–0.28)
Hindgut	2.07 (95 % CI 1.56–2.55)	4.52 (95 % CI 3.17–5.87)
Incidence rate of GI-NETs (per 100,000 population)	2.10 (95 % CI 1.56–2.54)	3.51 (95 % CI 2.50–4.53)
Foregut	0.64 (95 % CI 0.48–0.77)	1.20 (95 % CI 0.48–1.91)
Midgut	0.20 (95 % CI 0.15–0.24)	0.15 (95 % CI 0.12–0.18)
Hindgut	1.26 (95 % CI 0.94–1.52)	2.12 (95 % CI 1.56–2.67)

*Data modified from reference [5]

95 % CI 95 % confidence interval; *Foregut* esophagus, stomach and duodenum; *Midgut* jejunum, ileum and vermiform appendix; *Hindgut* large intestine and colon

Table 6 Percentages of distant metastases, associated MEN-1 and carcinoid syndrome in gastrointestinal neuroendocrine tumors (GI-NETs) in 2010

	Distant metastases (%)			Associated MEN-1 (%)	Carcinoid syndrome (%)
	Total	NET G1/G2	NEC		
Total GI-NETs	6.0	2.7	32.3	0.42	3.2
Foregut	8.6	1.8	40.9	0.72	1.1
Midgut	9.8	5.9	28.6	0	17.1
Hindgut	3.5	2.2	26.7	0.16	4.2

MEN-1 multiple endocrine neoplasia type 1

hindgut NETs, respectively; this indicates complications with MEN-1 in GI-NETs are rare in Japan.

In addition, the frequency of carcinoid syndrome in patients with GI-NETs was 3.2 %. Thus, carcinoid syndrome in GI-NETs is observed less frequently in Japan than Western nations. Regarding location, midgut NETs were the most common (17.1 %) followed by foregut NETs (4.2 %) and hindgut NETs (1.1 %).

Discussion

The second nationwide epidemiological survey of patients with GEP-NETs was conducted in Japan in 2010, and the data were compared with those from 2005 to elucidate epidemiological changes.

An estimated 3,379 patients received treatment for PNETs from January 1 to December 31, 2010 in Japan; therefore, the prevalence of PNETs is about 2.69 per 100,000 people. In 2005, these figures were 2,845 and 2.23 per 100,000 people, respectively, indicating an approximately 1.2-fold increase in the number of patients. The incidences of new-onset PNETs in 2005 and 2010 were about 1.01 and 1.27 per 100,000 people, respectively, indicating a 5-year increase in the incidence of new-onset PNETs. Interestingly, the percentage of NF-PNETs increased from 42.8 % in 2005 to 65.5 % in 2010, approaching that of Western nations [2, 7, 8]. There are 2 possible reasons for this. First, the disease concept of NETs disseminated among general clinicians; that is, clinicians have become accustomed to keeping PNETs in mind when treating pancreatic tumors. Second, the availability of endoscopic ultrasonography (EUS), which is useful for the diagnosis of pancreatic diseases [9, 10], has made endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) easy to perform for pancreatic tumors, which were merely being followed-up before; thus, the pathological diagnosis of PNETs has become more accurate [11, 12].

An estimated 8,088 people received treatment for GI-NETs in Japan in 2010, which means the prevalence of patients with this disease was about 6.42 per 100,000 people; in 2005, these figures were 4,406 and 3.45 per 100,000 people, respectively, indicating a 1.8-fold increase in the number of patients with this disease. In addition, the incidence rate of new-onset GI-NETs increased from about 2.1 per 100,000 people in 2005 to about 3.51 per 100,000 people in 2010.

Similar to the 2005 survey, few patients had midgut NETs and the locations of GI-NETs varied: 26.1, 3.6, and 70.3 % in the foregut, midgut, and hindgut, respectively. In Western nations, 30–60 % of GEP-NETs are derived from midgut [2, 13, 14] in contrast to the Japanese data. The epidemiology of GEP-NETs was recently reported in Asian nations including Taiwan [15], China [16], and Korea [17, 18]. Interestingly, the prevalence of patients with midgut NETs in these nations is low like Japan, indicating ethnic differences between Asians and Western populations.

The present study involved a survey conducted according to the 2010 WHO classification [6]. The 2010 WHO classification distinguishes between well-differentiated NETs and poorly differentiated NECs of small- or large-cell type. NETs are further divided with respect to Ki-67 index: NET G1 and NET G2. Before the present survey was conducted, the frequency of NEC among GEP-NETs in Japan was not clear. A Korean study [17] reports that the frequency of NECs among all GEP-NETs is 2.84 %. Meanwhile, in the present survey, the frequency of NEC among all GEP-NETs in Japan was 6.7 % (225/3,366). Interestingly, the frequency of NEC in NF-PNETs was 9.7 %, which is substantially higher than that reported in Western nations, where NEC in NF-PNETs is uncommon [8]. However, with regard to the grade of WHO calcification, the percentage of distant metastases in patients with NEC at initial diagnosis was high compared with that in patients with NET G1/G2. Especially, NF-PNETs patients with NEC was the most prevalent at the rate of 51.9 %. On the other hand, the frequency of NEC among all GI-NETs was 6.2 % in the present study; the common types were foregut NEC (12.6 %), midgut NETs (9.1 %), and hindgut NETs (2.3 %). Similarilly, the percentage of distant metastases in patients with NEC at initial diagnosis was high compared with that in patients with NET G1/G2.

According to the US SEER study, distant metastases are present in 64 % of PNETs followed by cecal, colonic, and small-intestinal NETs in 44, 32, and 30 % of PNETs, respectively [6]. In European and American referral centers, up to 77 and 91 % of patients with PNETs and intestinal NETs [19–22] present with distant metastases at initial diagnosis, respectively [13]. In the present Japanese study, patients in whom distant metastases were observed at initial diagnosis accounted for 19.9 % of PNETs and

6.0 % of GI-NETs. Regarding the location of GI-NETs, midgut NETs were the most common (9.8 %) followed by foregut NETs (9.8 %) and hindgut NETs (3.5 %); however, these frequencies are substantially lower than those reported in Western nations. Furthermore, as shown in Table 6, the frequency of carcinoid syndrome in patients with GI-NETs is low (3.2 %) compared to that reported in Western nations, suggesting ethnic differences.

At present, 4 genetic diseases—MEN-1, von Hippel-Lindau (VHL) disease, von Recklinghausen disease, and tuberous sclerosis—are thought to be associated with NETs [23]. As for PNETs complicated with MEN-1 [24, 25] or VHL, [26], screening must be performed at the initial diagnosis of PNETs because of different surveillance methods and treatment guidelines. MEN-1 is reported to be complicated with NF-PNETs, gastrinoma, and insulinoma at frequencies of about 80 %, 50 %, and 20 %, respectively [23]. On the other hand, 20–25 % of gastrinomas and 4–5 % of insulinomas are reported to be complicated with MEN-1 [27]. The rate of MEN-1 association in functional PNETS in the present study (4.9 %) does not differ from that reported in Western nations [27, 28]. However, MEN-1 associated with NF-PNETs was observed in only 4.0 % of cases in Japan. Furthermore, the presence of MEN-1 in GI-NETs in the present study was only 0.7 %, whereas approximately 30 % of NF-PETs are reported to be associated with MEN-1 in Western nations [28]. The difference in the frequencies of MEN-1 in NF-PETs and GI-NETs between Japan and Western nations may be due to ethnic differences as well.

There is currently no consensus regarding antitumor chemotherapy drugs against advanced GEP-NETs in Japan, and most treatment regimens are not covered by insurance. Global clinical studies on various molecularly targeted drugs against GEP-NETs were recently conducted. The results show everolimus [29, 30], an mTOR inhibitor, and sunitinib [31, 32], a multikinase inhibitor, are effective against advanced PNETs (NET G1/G2); in addition, octreotide LAR was shown to be effective against midgut-derived, metastatic, well-differentiated NETs in 2009 (PROMID study) [33]. These drugs have become reimbursable as antitumor drugs for treating advanced GI-NETs in Japan. Regarding NET, functionality, invasion depth, and the presence or absence of metastases must be correctly evaluated and treatment administered on the basis of the degrees of differentiation and malignancy of the tumor [4, 34–36]. Although surgical total excision is the standard treatment [37], some studies report that when radical treatment is difficult, debulking surgery of primary lesions and liver metastatic lesions effectively alleviate symptoms and improve prognosis [4, 34, 37]. On the other hand, in cases of unresectable advanced tumors, treatment aiming to improve prognosis by inhibiting tumor growth and improving clinical symptoms is necessary [8, 13, 27]. For this purpose, it is important to understand patient backgrounds, particularly epidemiological background, and be aware of the epidemiological differences between Japanese and Western populations. Thus, the results of the present epidemiological survey investigating the 5-year changes in GEP-NETs in Japan will be invaluable to clinicians.

Acknowledgments This study was supported in part by Grants-in-Aid from the National Cancer Center Research and Development Fund (Grant Number: 21-8-6). The authors are very grateful to the doctors who responded to the questionnaires.

Conflict of interest The authors declare that they have no conflict of interest.

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GEP-NETの腫瘍概念の変遷と本邦診療ガイドラインについて

Changing concept of neuroendocrine tumor and the first issue of Japanese treatment guidelines for pancreato-gastrointestinal neuroendocrine tumor.

関西電力病院 学術顧問/同 神経内分泌腫瘍センター長
今村正之

【ポイント】

◆ Oberndorfer が NET を①境界明瞭，②転移せず，③成長緩慢で有意の大きさに達せず，④良性である，と記載してカルチノイドと名付けた．その後，リンパ節転移，肝転移をきたすことが明らかになった．

◆ NET は①機能性か非機能性か，②遺伝性疾患に併存しているか否か，を鑑別して，③ Ki67 指数の測定をして，④全身を精査したうえで治療することが重要である．

◆ NET ガイドラインは文献の精査と専門家の討論の結果作成されたが，NET は希少疾患に属していて，種々の治療法の予後に対する効果が科学的に証明されていない．

◆ 日本神経内分泌腫瘍研究会が 2014 年末から NET 患者登録事業を始めた．ここに多くの患者が登録されれば，未解決の臨床的課題の解決に向けて前進できる．診察したら，登録をお願いしたい．

臨外　70(4)：388～396，2015

NETの病理学的概念の変遷と研究の歴史

神経内分泌腫瘍（NET）の歴史は，1907 年にドイツの若い病理学者 Oberndorfer[1] が小腸の NET をカルチノイドと命名したときに始まる．彼が当初，本腫瘍は①境界明瞭，②転移せず，③成長緩慢で有意の大きさに達せず，④良性である，と記載した[2]．その後，彼は転移するものがあることを報告したが，響きの良いこの名称が 100 年間人口に膾炙されて，一般医師の間では良性腫瘍との認識が続いてきた[2]．1940 年ごろから複数の論文で，本質的に悪性で misnomer であると指摘されていて，曾我ら[3] は 1970 年代に，消化管 NET は発生時から粘膜上皮層内内分泌細胞が粘膜下に浸潤して増殖し，腫瘍を形成することを指摘して，本質的に悪性と述べた．免疫染色法による病理診断が普及して正確な診断がなされるようになったために，臨床的にも早期のリンパ節転移，肝転移をきたすことが明らかになるとともに，国際的にも本質的に悪性と認識したうえでの病理分類作成の機運が高まり，2000 年の WHO Classification of Tumors of Digestive System（Lyons，France）では，カルチノイドという病名が消えた．

一方で，1960 年代から発展した膵・消化管ホルモンの研究が 1970 年代に最盛期を迎えた．Radioimmunoassay の開発により血中ホルモンの微量測定法が確立され，消化器系臓器間のホルモン調節の定量的研究が進み，グルカゴンの蛋白異化作用や，ソマトスタチンのホルモン分泌抑制作用も解明され[4]，免疫染色法の進歩により消化管粘膜上皮に存在する種々の内分泌細胞の同定が進み，homeostasis 維持における消化管ホルモンの役割が解明されていった．Pearse ら[5] は，消化管や膵のみならず全身に分布する一群の内分泌細胞を APUD 細胞と名付け，それから発生する腫瘍（NET）を APUDoma と呼んだ．

臨床的には，原因ホルモンが不明であった WDHA 症候群が血管作動性腸管ポリペプチド（VIP）により惹起されることを Bloom らが証明した．長らく根治

胆と膵 Vol. 36 (6) p. 593～595, 2015

膵内分泌腫瘍の診断・治療の新展開

日本神経内分泌腫瘍研究会（JNETS）の発足とNET登録の開始

今村　正之[1,2)]

要約：日本神経内分泌腫瘍研究会（JNETS）の設立経緯と事業内容について記した。神経内分泌腫瘍（NET）の診療上の課題に関しては，エビデンスに基づくコンセンサスが少なく，今後の臨床研究に待たなければならない。希少疾患であるNETの臨床研究についてはJNETSが主導することが望ましく，そのためにNET患者の悉皆登録を2年前にさかのぼって開始した。神戸市の先端医療振興財団の臨床研究情報センター（TRI）と契約して登録作業と統計解析については信頼している。その基本台帳的な登録作業の上に，臨床研究を立ち上げる予定である。課題を施設会員から公募して，遂行責任者が決まり，神戸市の先端医療振興財団の臨床研究情報センター（TRI）の協力を得て，論文作成を完成させる体制が整ったといえる。詳細に関しては，合わせてJNETSのホームページをお読みいただきたい。

Key words：日本神経内分泌腫瘍研究会，膵・消化管NET診療ガイドライン，NET登録事業

はじめに

NETは臨床症状が多彩であり，エビデンスに基づく診療の標準化のためには多くのデーターの解析が求められる。しかし，NETは希少疾患に属するために，データーの収集は容易でなく，臨床試験の実施も難しい。NET診療の標準化のためには表1に示すように診療ガイドラインの作成が必要である。また，公的な研究会組織を設立して，学術活動をすることが望ましい。

現在，EUや米国からNET診療ガイドラインが公表されていて，とくにEUではENETSという研究会が発足して，臨床研究活動が活発である。本邦においても約10年前からNET Work JapanというNETに関心を持ち続けている研究者の集まりが形成されて，年1回の学術集会が開かれ，症例報告やシンポジウム，招待講演に800名を超える参加者が集まった。NETの診断と治療に関しては，未解決の課題が多い。例えば，NETの治療の第1選択は切除術であるが，どのような術式が最善であるかに関して結論は得られていない（表2）。また，遠隔転移を有している患者に対して，外科的切除以外治療薬の少なかった時と比べて，現在は，いくつかの治療薬が承認されている。それらをどのように組み合わせて治療していくのが最善であるか，などの課題に対する回答を得るためには，早急に臨床研究を立ち上げる必要がある。そのような背景の下に2012年9月に日本神経内分泌腫瘍研究会（JNETS）が設立された。以下，JNETSの活動，とくに，登録事業について述べたい。

Ⅰ．日本神経内分泌腫瘍研究会（JNETS）について[1)]

JNETSは2012年9月に設立された（表3）。NETは全身に発生するが，とくに腹部の消化器と胸部の呼吸器・胸腺に多いので，理事には外科学会や消化器病学会，内分泌学会，病理学会の責任ある地位におられて，

Establishment of Japan Neuroendocrine Tumor Society and Registration of Japanese Patients with Neuroendocrine Tumors

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THE JOURNAL OF DERMATOLOGY

doi: 10.1111/1346-8138.12972

Journal of Dermatology 2015; **42**: 954–961

ORIGINAL ARTICLE

Sentinel lymph node biopsy for 102 patients with primary cutaneous melanoma at a single Japanese institute

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ABSTRACT

Sentinel lymph node biopsy (SLNB) is a widely accepted standard procedure for patients with clinically localized melanoma. Melanoma prevalence and Clark's subtype differ between Asians and Caucasians. Here, we evaluated our experience on SLNB for cutaneous melanoma in a Japanese population. SLNB was performed for patients with melanoma between July 2000 and June 2014. We retrospectively analyzed 102 patients regarding association of clinicopathological features with sentinel lymph node (SLN) status, melanoma-specific survival (MSS) and disease-free survival (DFS). A positive SLN was significantly associated with primary Breslow thickness. Compared with 43 patients with negative SLN, 59 patients with positive SLN had significantly shorter MSS (5-year survival rate, 94.3% vs 63.2%; $P = 0.0002$) and DFS (5-year survival rate, 92.7% vs 63.4%; $P = 0.0004$). According to our subgroup analyses, nine patients with positive non-SLN had significantly shorter MSS compared with 32 patients with negative non-SLN (5-year survival rate, 32.4% vs 68.5%; $P = 0.0273$). The survival of 51 Japanese patients with acral lentiginous melanoma (ALM) was not inferior to the survival of patients with other Clark's subtype. Breslow thickness is an important factor for both MSS and DFS, and the status of SLN is the most predictive prognostic factor in Japanese patients with clinically localized melanomas, as in case of Caucasians. Features of ALM may be different between Asians and Caucasians.

Key words: clinically localized melanoma, disease-free survival, melanoma, melanoma-specific survival, sentinel lymph node biopsy.

INTRODUCTION

Involvement of regional lymph nodes is the most important prognostic factor for survival and recurrence among individuals with cutaneous melanoma.[1–4] Since the first report by Morton *et al.*[1] in 1992, numerous studies have proven the prognostic value of sentinel lymph node biopsy (SLNB),[2,5–9] and the American Joint Committee on Cancer has recommended SLNB for patients with certain types of melanoma, such as thick (>1 mm) or ulcerated melanomas.[10] However, compared with Western countries, in Asian countries, where melanoma is relatively uncommon, few studies on the use of SLNB[11–17] have been conducted. In addition to differences in prevalence, Asians and Caucasians differ in terms of Clark's subtype. Among Caucasians, superficial spreading melanoma is the most common subtype and acral lentiginous melanoma (ALM) is the fourth common subtype.[18,19] In contrast, ALM is the most common subtype among Asians and it has a worse prognosis for Caucasians compared with other Clark's subtype.[18,20,21]

The objectives of the present study were to investigate the clinical usefulness of SLNB and to evaluate the outcomes based on the status of SLN among Japanese patients with clinically localized cutaneous melanoma.

METHODS

Patients

This was a retrospective study of 107 patients who underwent SLNB for cutaneous melanoma at Okayama University Hospital between July 2000 and June 2014. Patients with melanoma *in situ* ($n = 5$) and those with clinical or radiographic evidence of lymph node and visceral metastases were excluded.

Sentinel lymph node biopsy has been performed for patients with cutaneous melanoma at Okayama University Hospital since 1999; however, these procedures were performed by dye method alone, which has a poor SLN detection rate. Since 2000, the method for SLNB included a combination of dye, radioisotope and gamma probe; the study period included procedures that used this combination.

The clinicopathological features and outcomes of the study population were reviewed. Variables recorded were sex, age, location, Clark's subtype, Breslow thickness, tumor (T) stage, presence of ulceration, Clark level, number of SLN, relapse and outcomes. Written informed consent for SLNB was obtained from all patients and this study was approved by the institutional ethics committee of Okayama University.

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Received 3 April 2015; accepted 29 April 2015.

THE JOURNAL OF DERMATOLOGY

doi: 10.1111/1346-8138.12299

Journal of Dermatology 2014; **41**: 3–10

ORIGINAL ARTICLE

Cutaneous lymphoma in Japan: A nationwide study of 1733 patients

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ABSTRACT

Types of cutaneous lymphoma (CL) and their incidences may vary among geographic areas or ethnic groups. The present study aimed to investigate the incidences of various CL in Japan, using epidemiological data from a nationwide registration system for CL. Between 2007 and 2011, 1733 new patients with CL were registered from over 600 dermatological institutes in Japan. The 1733 patients registered included 1485 (85.7%) patients with mature T- and natural killer (NK)-cell neoplasms, 224 (12.9%) with B-cell neoplasms and 24 (1.4%) with blastic plasmacytoid dendritic cell neoplasm. Mycosis fungoides (MF) is the most common CL subtype in the present study (750 patients, 43.3%). The proportion of MF patients with early-stage disease was 73%, similar to that of previous studies from other cohorts. The incidence rates of adult T-cell leukemia/lymphoma and extranodal NK/T-cell lymphoma, nasal type were 16.7% and 2.0%, respectively, which may account for the higher incidence of mature T- and NK-cell neoplasms in Japan, as compared with that in the USA and Europe. A male predominance was observed in most types of CL, except for several CL subtypes such as subcutaneous panniculitis-like T-cell lymphoma.

Key words: adult T-cell leukemia/lymphoma, cutaneous lymphoma, extranodal natural killer/T-cell lymphoma, mycosis fungoides, nasal type, subcutaneous panniculitis-like T-cell lymphoma.

INTRODUCTION

Cutaneous lymphomas (CL) are the second most common type of extranodal non-Hodgkin's lymphoma, after gastrointestinal lymphomas.[1] CL are defined as lymphomas with skin infiltration of neoplastic lymphocytic cells, without nodal or internal involvement at diagnosis. The World Health Organization (WHO) classification for tumors of hematological and lymphoid tissue, including CL, was published in 2008, through several consensus meetings, and is based on a combination of clinicopathological, phenotypic, genetic and molecular characteristics.[2] Mycosis fungoides (MF) is the most common type of CL. In 2007, a revised version of the MF/Sézary syndrome (MF/SS) staging system was published, thereafter, a tumor–node–metastasis (TNM) classification system was proposed for CL other than MF/SS.[3,4] Using the new criteria, clinical outcomes including survival data have recently been reported from the UK and Japan.[5,6] However, these studies analyzed clinical data from only a single medical center over 25- or 30-year periods.

Cutaneous lymphoma is a rare disease entity, and is difficult to study on a large scale. Thus, most epidemiological surveys on CL have been limited to case series reports, mainly of single medical centers.[7–12] Epidemiologic data of CL has not been fully evaluated to date. Entry of data into a comprehensive registry of CL is required in many parts of the world. To date, a few large-scale epidemiological studies on CL have been performed mainly in the USA and Europe.[13–15] The findings from the present study, including the incidence rates of CL, may be somewhat different from those studies. Indeed, the incidence pattern of CL has been reported to be different by country or ethnic group, like that of gross lymphoproliferative disorders. For example, adult T-cell leukemia/lymphoma (ATLL) is endemic in southwest Japan, especially on Kyushu Island.[16,17] However, it is very rare in the USA and Europe.[13–15]

In 2007, we established a nationwide registry system for Japanese CL, in cooperation with the Japanese Skin Cancer Society (JSCS) Lymphoma Study Group. The present registry covers the whole country, and is aimed at elucidating the distinct pattern of Japanese CL, mainly using the WHO classification and the revised version of MF/SS clinical staging.[2,3] In addition, the present registry can minimize the kind of selection bias resulting from single-center analysis because data from hundreds of institutions throughout Japan are included. Such analyses will be conducted over the whole area of Japan each year. Thus, this registry will facilitate further clinical study and basic research in the near future.

METHODS

We analyzed the incidence pattern of CL from 2007 to 2011. The present registry covers the entire nation and includes more

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Received 30 April 2013; accepted 27 August 2013.

than 600 dermatological institutes throughout Japan, all of which have been approved as residency programs for board-certified dermatologists by the Japanese Dermatological Association (JDA) (Table 1). On average, a total of 628 institutes per year participated in the present study. In addition, the total number of the registered institutes of each prefecture is shown in Table 1. The diagnosis of CL was confirmed according to the WHO classification mentioned above.[2] Subjects were newly diagnosed patients with CL in each institute. Clinical data including age at diagnosis, sex, TNM classification, clinical stage, anatomical site of the primary lesion, nodal or extracutaneous involvement, and initial therapy were retrieved from the medical database of each medical institute. In the present study, unconventional sites such as the groin were excluded from the statistical analyses, because of their small number. Those data were submitted electronically without personal information to our data center once a year. This study was approved by the ethics board committee (the review board of the JDA).

Table 1. Distribution of dermatological institutes

	Dermatological institutes (2007–2011)		
	Total no.	No. per year	%
Prefecture	3140	628	100
Hokkaido	157	31	5.0
Aomori	32	6	1.0
Iwate	29	6	0.9
Miyagi	54	11	1.7
Akita	22	4	0.7
Yamagata	21	4	0.7
Fukushima	39	8	1.2
Ibaraki	52	10	1.7
Tochigi	32	6	1.0
Gunma	40	8	1.3
Saitama	133	27	4.2
Chiba	79	16	2.5
Tokyo	397	79	12.6
Kanagawa	227	45	7.2
Niigata	33	7	1.1
Yamanashi	17	3	0.5
Nagano	52	10	1.7
Toyama	44	9	1.4
Ishikawa	49	10	1.6
Fukui	27	5	0.9
Gifu	63	13	2.0
Shizuoka	124	25	3.9
Aichi	231	46	7.4
Mie	33	7	1.1
Shiga	53	11	1.7
Kyoto	76	15	2.4
Osaka	249	50	7.9
Hyogo	143	29	4.6
Nara	41	8	1.3
Wakayama	30	6	1.0
Tokushima	20	4	0.6
Kagawa	23	5	0.7
Ehime	15	3	0.5
Kochi	22	4	0.7
Tottori	10	2	0.3
Shimane	20	4	0.6
Okayama	46	9	1.5
Hiroshima	88	18	2.8
Yamaguchi	38	8	1.2
Fukuoka	110	22	3.5
Saga	20	4	0.6
Nagasaki	33	7	1.1
Kumamoto	41	8	1.3
Oita	24	5	0.8
Miyazaki	18	4	0.6
Kagoshima	17	3	0.5
Okinawa	16	3	0.5

The comprehensive classification of CL and hematopoietic neoplasms with marked affinity for the skin was presented by the European Organization for Research and Treatment of Cancer (EORTC) in 2005.[13] This framework of CL classification was essentially duplicated by the WHO classification, with several nominal or hierarchical differences.[2] The present registry has dealt with CL, shown in Table 2. Clinical stage and TNM classification of patients with MF/SS were identified using the International Society for Cutaneous Lymphomas (ISCL)/EORTC proposal in 2007 (which was modified in 2011).[3,18]

RESULTS

In total, 1733 patients with CL have been registered between 2007 and 2011 (Table 2). The patients ranged 1–100 years (median, 65) in age, and included 978 males and 751 females (M : F ratio, 1.30). Mature T-cell and natural killer (NK)-cell neoplasm was the most common type of CL, accounting for 1485 (85.7%) patients. Next in prevalence, 224 (12.9%) of 1733 patients had mature B-cell neoplasm. The remaining 24 (1.4%) patients had blastic plasmacytoid dendritic cell neoplasm (BPDN).

Mycosis fungoides was the most common subtype of mature T-cell and NK-cell neoplasms, comprising 50.5% of cases, followed by ATLL (290 patients, 19.5%), primary cutaneous $CD30^+$ T-cell lymphoproliferative disorders (208 patients, 14.0%), and peripheral T-cell lymphoma, not otherwise specified (100 patients, 6.7%). Other subtypes of mature T-cell and NK-cell neoplasms included 34 (2.3%) subcutaneous panniculitis-like T-cell lymphoma (SPTCL), 34 (2.3%) extranodal NK/T-cell lymphoma, nasal type (ENKL) and 33 (2.2%) SS cases. The incidences of rare disease entities including primary cutaneous $CD4^+$ small/medium T-cell lymphoma, primary cutaneous $\gamma\delta$ T-cell lymphoma and primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma were 25 (1.7%), five (0.3%) and six (0.4%), respectively.

The most common mature B-cell neoplasm subtype was primary cutaneous diffuse large-cell lymphoma, leg type (95 patients, 42.4%), followed by extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) (72 patients, 32.1%), primary cutaneous follicle center lymphoma (pcFCL) (37 patients, 16.5%) and intravascular large B-cell lymphoma (IVLBCL) (20 patients, 8.9%).

Table 2. Characteristics of cutaneous lymphomas between 2007 and 2011

	Total		Neoplasm	Male	Female		Age at diagnosis (years)		
	n	%	category (%)	*n*	*n*	M : F	Median	Average ± SD	Range
Total	1733	100.0		978	751	1.30	65	63.1 ± 16.5	1–100
Mature T-cell and NK-cell neoplasms	1485	85.7	100.0	838	643	1.30	64	62.2 ± 16.4	5–100
Mycosis fungoides	750	43.3	50.5	438	310	1.41	62	60.6 ± 15.5	13–95
Sézary syndrome	33	1.9	2.2	26	7	3.71	68	67.6 ± 12.3	37–89
Primary cutaneous $CD30^+$ T-cell lymphoproliferative disorders	208	12.0	14.0	117	91	1.29	63	59.4 ± 20.4	6–97
Primary cutaneous anaplastic large-cell lymphoma	136	7.8	9.2	84	52	1.62	67.5	63.5 ± 19.1	12–97
Lymphomatoid papulosis	66	3.8	4.4	30	36	0.83	53.5	51.1 ± 20.4	6–84
Subcutaneous panniculitis-like T-cell lymphoma	34	2.0	2.3	12	22	0.55	55	54.5 ± 16.3	17–81
Peripheral T-cell lymphoma, NOS	100	5.8	6.7	51	47	1.09	68	65.5 ± 18.4	5–100
Primary cutaneous $CD4^+$ small/medium T-cell lymphoma*	25	1.4	1.7	11	14	0.79	65	61.5 ± 20.7	14–90
Primary cutaneous γδ T-cell lymphoma	5	0.3	0.3	2	3	–	–	–	–
Primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma*	6	0.3	0.4	1	5	–	–	–	–
Extranodal NK/T-cell lymphoma, nasal type	34	2.0	2.3	13	21	0.62	66	65.6 ± 15.4	31–94
Adult T-cell leukemia/lymphoma	290	16.7	19.5	167	123	1.36	68	67.5 ± 11.9	19–91
Mature B-cell neoplasms	224	12.9	100.0	120	104	1.15	70	68.3 ± 16.2	1–94
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue	72	4.2	32.1	36	36	1.00	63	63.4 ± 16.7	20–94
Primary cutaneous follicle center lymphoma	37	2.1	16.5	25	12	2.08	64	67.1 ± 14.7	26–88
Primary cutaneous diffuse large-cell lymphoma, leg type	95	5.5	42.4	45	50	0.90	77	72.5 ± 16.7	1–92
Intravascular large B-cell lymphoma	20	1.2	8.9	14	6	2.33	70	72.4 ± 15.7	53–85
Immature hematological neoplasms†									
Blastic plasmacytoid dendritic cell neoplasm	24	1.4	–	20	4	5.00	77.5	74.5 ± 11.5	34–86

*Provisional. †Immature hematological neoplasms include "acute myeloid leukemia and related precursor neoplasms" and "precursor lymphoid neoplasms". NK, natural killer; NOS, not otherwise specified; SD, standard deviation.

A male predominance was observed in all CL (M : F ratio, 1.30), with over twofold male predominance for BPDN (M : F ratio, 5.00), SS (M : F ratio, 3.71), IVLBCL (M : F ratio, 2.33) and pcFCL (M : F ratio, 2.08). In contrast, a female predominance was observed in SPTCL (M : F ratio, 0.55), followed by in ENKL (M : F ratio, 0.62), primary cutaneous $CD4^+$ small/medium T-cell lymphoma (M : F ratio, 0.79) and lymphomatoid papulosis (LyP) (M : F ratio, 0.83).

The median age at diagnosis was low in patients with LyP (53.5 years) and SPTCL (55 years), as compared with that of all CL (65 years). In contrast, the median age at diagnosis was high in patients with BPDN (77.5 years) and primary cutaneous diffuse large-cell lymphoma (pcDLBCL), leg type (77 years). In general, the patient's age was high in mature B-cell neoplasm, as compared with those in mature T-cell and NK-cell neoplasm (median ages of 70 and 64 years, respectively). In reference to age distribution, bimodal distributions of age at diagnosis were found in LyP (the fourth and the sixth decades) and SPTCL (the fifth and the seventh decades).

Clinical stage of MF/SS (Table 3)

In terms of clinical staging, the 744 MF/SS patients included 229 (29.6%) with stage IA, 303 (39.1%) stage IB, 33 (4.3%) stage IIA, 86 (11.1%) stage IIB, 57 (7.4%) stage IIIA, seven (0.9%) stage IIIB, 17 (2.2%) stage IVA1, 28 (3.6%) stage IVA2 and 14 (1.8%) stage IVB. In all, 565 patients (73%) had early-stage disease (stage I + IIA). The remaining 209 (27%) patients had the advanced-stage disease (stage IIB + III + IV). A male predominance was observed in stage IIIA (M : F ratio, 4.18), stage IIIB (M : F ratio, 2.50) and stage IVA1 (M : F ratio, 2.40). In contrast, a female predominance was observed in stage IVA2 (M : F ratio, 0.75). The median ages at diagnosis were 61–62 years in stage IA to IIB and stage IIIB, and 64–70 years in stage IIIA and IV.

Anatomical site of the primary skin lesion (Fig. 1)

The skin lesion sites of primary cutaneous anaplastic large-cell lymphoma were distributed approximately evenly. The most commonly affected sites were the lower extremities in SPTCL