

# Surgical results of non-ampullary duodenal cancer: a nationwide survey in Japan

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## Abstract

**Background** As non-ampullary duodenal cancer is relatively rare, the optimal treatment strategy, including the appropriate surgical procedure and efficacy of adjuvant chemotherapy, remains unclear. This nationwide survey aimed to clarify the actual lymph node spread pattern and determine the optimal treatment strategy for this disease, using a large-scale database.

**Methods** We used a questionnaire and a retrospective registry of 1083 patients with non-ampullary duodenal cancer who had undergone surgery during 2008–2017 in 114 high-volume Japanese Society of Hepatobiliary and Pancreatic Surgery-certified training institutions. Propensity score-matched analyses were conducted to minimise background bias. Cox regression was performed to identify

covariates associated with recurrence-free survival. There were distinct disparities in the nodal dissection rate according to the predominant tumor location and tumor invasion depth. Metastases were frequently observed in the peripancreatic nodes and those along the superior mesenteric artery, irrespective of tumor location. Their dissection seemed to be beneficial for improved survival. In the overall cohort, no survival benefit was observed in patients who received adjuvant chemotherapy when compared with that in patients who underwent surgery alone. Nevertheless, in the matched cohort, adjuvant chemotherapy for > 6 months was associated with a significant improvement in recurrence-free survival (median: 43.5 vs. 22.5 months,  $p = 0.016$ ), particularly in patients with tumor invasion of the subserosa or deeper tumor invasion, lymph node

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metastasis, or elevated serum carbohydrate antigen 19-9 levels.

**Conclusion** Pancreatoduodenectomy should be the standard procedure for advanced non-ampullary duodenal cancer. Adjuvant chemotherapy for > 6 months, especially for advanced tumors, significantly improves survival.

**Keywords** Duodenal cancer · Pancreatoduodenectomy · Adjuvant chemotherapy

### Abbreviations

LR	Local resection
PD	Pancreatoduodenectomy
DG	Distal gastrectomy
is/M	Tumor in situ or tumor confined to the lamina propria
SM	Tumor confined to the submucosa
MP	Tumor invasion of the muscularis propria
SS	Tumor invasion of the subserosa
SE	Tumor invasion that is contiguous to or penetrates the serosa and is exposed to the peritoneal cavity
SI	Tumor invasion of adjacent structures
nos.	Number of lymph node stations
OS	Overall survival
RFS	Recurrence-free survival
HR	Hazard ratio
ASA	American Society of Anesthesiologists
CEA	Carcinoembryonic antigen
CA19-9	Carbohydrate antigen 19-9
CI	Confidence interval

### Introduction

Non-ampullary duodenal cancer is a relatively rare disease with no established treatment guidelines [1, 2]. It is generally acknowledged that surgical resection is the only potentially curative treatment. Due to anatomical reasons, surgical procedures vary drastically depending on tumor location and depth of invasion, and include local resection (LR), pancreatoduodenectomy (PD), distal gastrectomy (DG), and pancreas-preserving duodenectomy. Such diversity leads to significant differences in the type of reconstruction, mortality, morbidity, and postoperative quality of life [3–8]. In addition, unlike other gastrointestinal malignancies, the survival benefit of adjuvant chemotherapy for patients with non-ampullary duodenal cancer remains controversial [9–11].

Some meta-analyses and systematic reviews have focused on the treatment of duodenal cancer [1, 12–17]. However, the majority were retrospective, single-institutional, and small case series. We conducted a nationwide survey to investigate the optimal treatment strategy for non-ampullary duodenal cancer, aiming mainly to elucidate the precise lymph node spread pattern, determine the appropriate surgical procedure and extent of lymph node dissection according to both predominant tumor location and depth of invasion, and define the role of adjuvant chemotherapy using a large comprehensive database.

### Methods

#### Study design and population

This national questionnaire survey included patients with non-ampullary duodenal cancer who had undergone surgical treatment between January 2008 and December 2017. We selected Japanese Society of Hepatobiliary and Pancreatic Surgery-certified training institutions with high volumes of hepato-biliary-pancreatic surgeries because PD, the most frequently selected type of surgical resection for this disease, is often associated with a relatively high rate of complications. The study protocol was approved by the institutional ethical review boards of all participating hospitals. Informed consent for analysis was obtained from all participants by the opt-out approach.

#### Definitions

The duodenum is divided anatomically into four segments: first (superior segment), second (descending segment), third (horizontal segment), and fourth (ascending segment). Patients with third or fourth segment tumors were classified into a single group (third/fourth) due to small sample size. Pathological tumor depth was classified as follows: is/M, tumor in situ or tumor confined to the lamina propria; SM, tumor confined to the submucosa; MP, tumor invasion of the muscularis propria; SS, tumor invasion of the subserosa; SE, tumor invasion that is contiguous to or penetrates the serosa and is exposed to the peritoneal cavity; and SI, tumor invasion of adjacent structures. The number of lymph node stations (nos.) was determined according to the uniform definition of pancreatic carcinoma established by the Japan Pancreas Society [18]. Procedures performed included PD, DG, and LR of the duodenum. Lymph node dissection included systematic regional lymphadenectomy and limited lymph node dissection. Perioperative complications were assessed according to the Clavien–Dindo classification [19, 20]. The indication for adjuvant

chemotherapy and selection of the chemotherapeutic regimens were left to the discretion of physicians.

### Statistical analysis

All statistical analyses were performed using JMP software ver. 14.3 (SAS Institute Inc.). The final follow-up date was June 30, 2019. Overall survival (OS) was defined as the period from the time of surgery to the date of death from any cause or censoring until the date of the last follow-up. Recurrence-free survival (RFS) was calculated from surgery to the first detection of recurrence or earlier death of any cause. Data from patients who were alive without recurrence at the last follow-up were censored for the RFS analysis. Kaplan–Meier survival analysis and the corresponding log-rank tests were carried out to determine differences in survival rates. Categorical variables were compared using the  $\chi$ -squared test. Continuous variables were compared using the Mann–Whitney *U* test or Kruskal–Wallis test. The univariate and multivariate hazard ratios (HRs) were calculated using a Cox proportional hazard model.  $p < 0.05$  was considered statistically significant.

A matched cohort study using propensity score methodology was used to minimize the treatment bias associated with the administration of adjuvant chemotherapy. A propensity score for each patient was calculated by logistic regression using the co-variables known to affect postoperative outcomes. One-to-one propensity score-matched study groups were created using nearest-neighbor matching without replacement. A caliper of 0.20 multiplied by the standard deviation of the logit of the propensity score was used. Outcomes were compared between the two groups before and after propensity score matching.

We used a previously described method to evaluate the therapeutic benefits of lymph node dissection [21, 22]. The frequency of metastasis at each station was determined by dividing the number of patients with metastasis at that station by the number of patients in whom that station was dissected. The cumulative 5-year OS rate of patients with metastasis at each nodal station was calculated while discounting the presence/absence of metastasis at other stations. An index of the benefit gained by dissection at each station was calculated by multiplying the frequency of metastasis by the 5-year OS rate of patients with metastasis for each station. The index was not determined for stations that had not been dissected in all patients or in which no metastasis was reported in any patients in whom the station had been dissected. Similarly, we did not determine the index when all surviving patients with metastasis at the station had been censored within a 5-year period.

## Results

### Clinicopathological characteristics and survival outcomes

Among 230 Japanese Society of Hepatobiliary and Pancreatic Surgery-certified training institutions, 114 (49.5%) participated in this study, and 1083 patients were included in the analysis (Supplemental Fig. 1). Clinicopathological characteristics according to tumor invasion depth are presented in Table 1. The median follow-up duration was 38.3 months (0.2–137.8). The most frequent procedure in patients with SM or deeper invasion was PD, whereas LR was mostly performed in is/M patients. In addition, DG was performed for 79 patients (29%) of tumors predominantly located in the first segment (Supplemental Table 1). The rates of 30-day mortality after LR/DG/PD were 0/0/0.7%, respectively.

The 5-year OS and RFS rates were 70.8% and 69.5%, respectively. The survival curves were well stratified according to the depth of tumor invasion (Fig. 1). Furthermore, the median post-recurrence survival was 14.2 months (0.2–107.7). The 1-, 2- and 3-year post-recurrence survival rates were 55.0, 30.0 and 17.2%, respectively.

### Rates of lymph node dissection and metastasis according to tumor location

As the anatomical distribution of regional lymph nodes and the pattern of lymph node metastasis influence the choice of surgical procedure, we further evaluated the incidence of metastasis in each nos. The analysis was conducted on patients with advanced (MP or deeper) tumors because the rates of lymph node dissection and metastasis among patients with is/M tumors were very low. Patients with SM were independently evaluated because their rate of positive lymph node metastasis was non-negligible but still relatively low (Table 1, Supplemental Fig. 2 and Supplemental Fig. 3).

Overall, 10,183 lymph nodes from 599 patients with advanced cancer were analyzed; the median number of harvested lymph nodes per patient was 17 (0–88). Metastasis to at least one lymph node station was found in 363 patients (61.4%). The frequency of lymph node metastasis according to tumor location and depth of invasion is summarized in Fig. 2 and Supplemental Fig. 3. For cancers predominantly in the first or second segments, lymph nodes along the common hepatic artery and hepatoduodenal, infra-pyloric, and posterior pancreatic head nodes (nos. 8, 12, 6, 13) were usually dissected. Pancreatic nodes and nodes along the superior mesenteric artery were

**Table 1** Clinicopathological characteristics according to the depth of tumor invasion

	is/M (n = 398)	SM (n = 86)	MP (n = 71)	SS (n = 230)	SE/SI (n = 298)	p value
Age, years	66 (21–86)	71 (42–85)	70 (37–87)	67 (19–90)	66 (31–90)	< 0.001
Sex						0.101
Female	138 (35)	18 (21)	21 (30)	76 (33)	107 (36)	
Male	260 (65)	68 (79)	50 (70)	154 (67)	191 (64)	
BMI, kg/m <sup>2</sup>	22.3 (13.5–38.0)	22.2 (12.3–32.7)	22.5 (17.4–34.5)	21.8 (13.5–40.9)	22.2 (13.0–34.2)	0.215
ASA classification <sup>a</sup>						0.633
1–2	363 (91)	80 (93)	61 (87)	208 (90)	264 (89)	
≥ 3	34 (9)	6 (7)	9 (13)	22 (10)	32 (11)	
Tumor location						< 0.001
First segment	74 (19)	33 (38)	25 (35)	50 (22)	61 (21)	
Second segment	274 (68)	49 (57)	36 (69)	135 (58)	195 (65)	
Third/fourth segments	50 (13)	4 (5)	10 (14)	45 (20)	42 (14)	
CEA, U/mL	2.3 (0.5–11.4)	3.0 (0.8–44.2)	2.3 (0.5–16.3)	2.5 (0.2–47.9)	2.9 (0.4–285.0)	< 0.001
CA19-9, U/mL	9 (1–229)	9 (1–207)	9 (1–229)	16 (1–2915)	29 (1–67,700)	< 0.001
Surgical procedure						< 0.001
Pancreatoduodenectomy	157 (39)	42 (49)	53 (75)	195 (84)	281 (94)	
Local resection	214 (54)	21 (24)	8 (11)	21 (9)	14 (5)	
Distal gastrectomy	27 (7)	23 (27)	10 (14)	14 (6)	3 (1)	
Lymph node dissection	190 (48)	65 (76)	66 (93)	214 (93)	288 (97)	< 0.001
Morbidity ≥ Clavien–Dindo IIIa	91 (23)	26 (30)	24 (34)	73 (32)	110 (37)	< 0.001
30-day mortality	0 (0)	1 (1)	0 (0)	0 (0)	4 (1)	0.051
Tumor size, mm	23 (1–95)	18 (1–88)	30 (5–120)	40 (5–115)	41 (7–162)	< 0.001
Positive lymph node metastasis	6 (2)	12 (14)	26 (37)	122 (54)	215 (73)	< 0.001
No. of harvested lymph nodes	1 (0–56)	7 (0–50)	14 (0–42)	15 (0–74)	19 (0–88)	< 0.001
No. of metastatic lymph nodes	0 (0–2)	0 (0–6)	0 (0–5)	0 (0–19)	1 (0–56)	< 0.001
Histological differentiation type <sup>b</sup>						< 0.001
Differentiated	383 (96)	81 (94)	57 (80)	183 (80)	236 (79)	
Undifferentiated	14 (4)	5 (6)	14 (20)	47 (20)	62 (21)	
Residual tumor <sup>c</sup>						< 0.001
R0	390 (98)	82 (98)	68 (99)	217 (96)	267 (91)	
R1	8 (2)	2 (2)	1 (1)	10 (4)	28 (9)	
Adjuvant chemotherapy						
Initiated	4 (1)	4 (5)	17 (24)	98 (43)	155 (52)	< 0.001
> 6 months	4 (1)	3 (3)	12 (17)	59 (27)	90 (30)	< 0.001

Data are expressed as median (range) for continuous variables and number (percentage) for categorical variables

*BMI* body mass index (calculated as weight in kilograms divided by height in metres squared), *ASA* American Society of Anesthesiologists, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19–9, *is/M* tumor in situ or confined to the lamina propria, *SM* tumor confined to the submucosa, *MP* tumor invades the muscularis propria, *SS* tumor invades the subserosa, *SE* tumor invasion is contiguous to the serosa or penetrates the serosa and is exposed to the peritoneal cavity, *SI* tumor invades adjacent structure

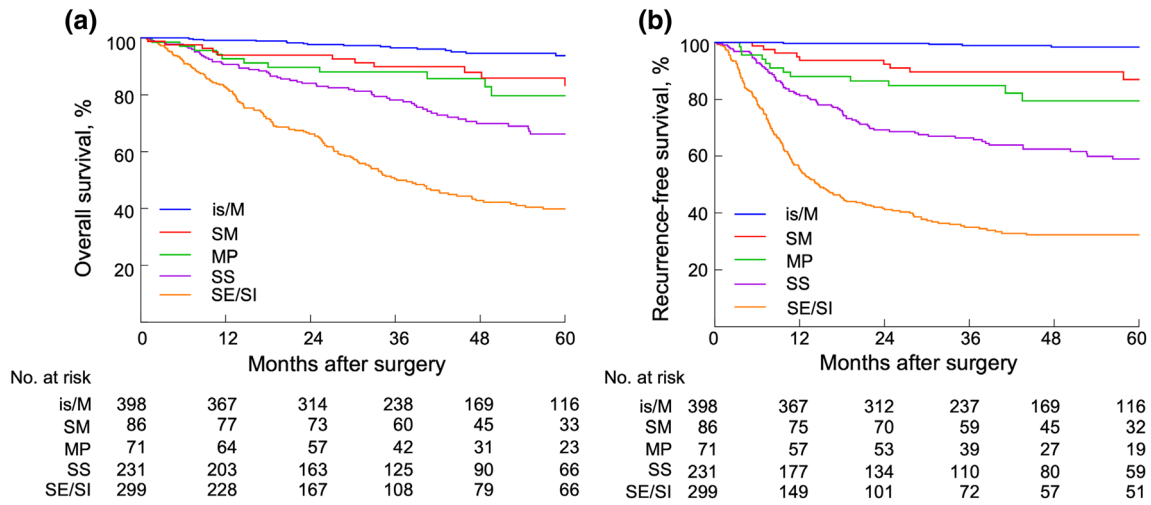
<sup>a</sup>Missing value for each variable: 4

<sup>b</sup>Missing value for each variable: 1. <sup>c</sup>missing value for each variable: 10

preferentially dissected in cancers predominantly in the third/fourth segments, while the frequency of dissection for nos. 8 and 6 remained below 50%. The frequency of nodal dissection along the left gastric artery and around the celiac

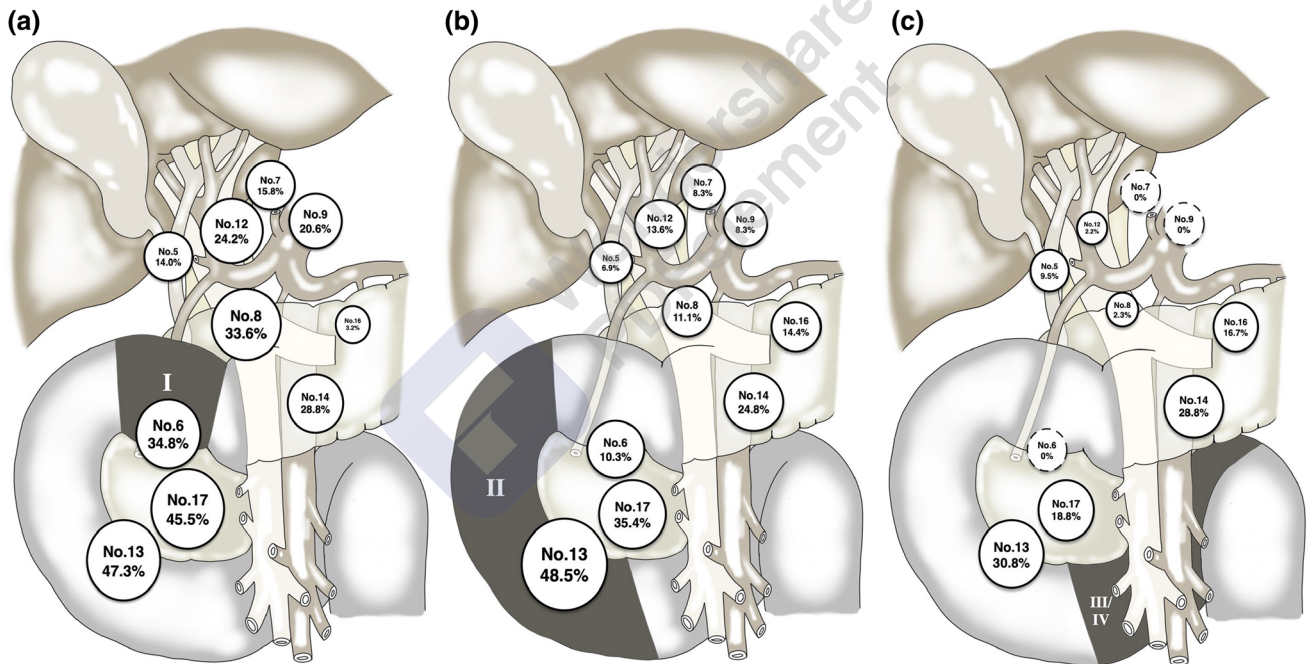
axis area (nos. 7, 9) was very low, regardless of tumor location or depth.

Metastasis rates were relatively high at nos. 13, 14, and 17 in all cancers. The rate of metastasis at nos. 6 was low, but not negligible in the first and second segments. The



**Fig. 1** Cumulative survival curves according to the depth of tumor invasion. **a** Overall and **b** recurrence-free survival analysis. is/M tumor in situ or confined to the lamina propria, SM tumor confined to the submucosa, MP tumor invades the muscularis propria, SS tumor

invades the subserosa, SE tumor invasion is contiguous to the serosa or penetrates the serosa and is exposed to the peritoneal cavity, SI tumor invades adjacent structure



**Fig. 2** Distribution of lymph node metastasis in MP or deeper non-ampullary duodenal cancer according to tumor location. **a** the first segment ( $n = 136$ ), **b** the second segment ( $n = 366$ ), **c** the third/fourth segments of the duodenum ( $n = 97$ ) No.5, supra-pyloric; No.6, infra-pyloric; No.7, left gastric artery; No.8, along the common hepatic

artery; No.9, around the celiac axis; No.12, hepatoduodenal; No.13, posterior pancreatic head; No.14, along the superior mesenteric artery; No.17, anterior pancreatic head; No.16, para-aortic lymph nodes

rates of metastasis at nos. 5, 7, and 9 were extremely low and unrelated to tumor location or depth. However, this might be a reflection of their low dissection rates.

**Estimated survival benefit of nodal dissection**

Table 2 shows the frequency of lymph node metastases, 5-year OS rate for involvement at each nodal station, and survival benefit index of advanced cancer (MP/SS/SE/SI) according to tumor location. For tumors predominantly in the second segment, the index was highest for nos. 13

followed by 17 and 14. The index values for these stations were also high in cancers predominantly located in the first segment. The frequency of metastases in those stations was equivalent, even in III/IV segment-predominant cancer, while the index values were low despite the optimal cut-off value not being clear. For cancers predominantly in the first segment, the index values were also high in nos. 6, 12, and 8. In contrast, the index value of para-aortic lymph nodes was very low in all cancers.

### Impact of adjuvant chemotherapy for non-ampullary duodenal cancer

Adjuvant chemotherapy was administered to 278 (25.7%) patients. The most frequent regimen was S-1 monotherapy ( $n = 220$ ), followed by capecitabine plus oxaliplatin ( $n = 24$ ), modified FOLFOX6 (fluorouracil, leucovorin, and oxaliplatin,  $n = 15$ ), S-1 plus gemcitabine ( $n = 3$ ), S-1 plus irinotecan ( $n = 3$ ), tegafur/uracil ( $n = 3$ ), capecitabine monotherapy ( $n = 2$ ), gemcitabine monotherapy ( $n = 2$ ), S-1 plus oxaliplatin ( $n = 2$ ), paclitaxel monotherapy ( $n = 1$ ), 5-FU monotherapy ( $n = 1$ ), irinotecan plus bevacizumab ( $n = 1$ ), and S-1 plus cisplatin ( $n = 1$ ). Median duration of treatment was 7.4 months (0.1–64.4).

In the overall cohort, there were significant differences in age, ASA classifications, tumor location, CA19-9 level, surgical procedure, rate of lymph node dissection, tumor size, tumor depth, rate of positive lymph node metastasis, histological differentiation type, residual tumor between

patients with and without adjuvant chemotherapy administration. To control for treatment bias, one-to-one propensity score matching was performed using these covariables, creating 188 well-balanced pairs of patients (Table 3). In the overall cohort, the RFS of patients who started adjuvant chemotherapy and received it for over 6 months was shorter than those who underwent surgery alone or received adjuvant chemotherapy for less than 6 months (median RFS 28.8 months vs. not reached,  $p < 0.001$ ; Supplemental Fig. 4a and 44.1 months vs. not reached,  $p < 0.001$ ; Supplemental Fig. 4b). In the matched cohort, there was no difference in RFS between patients who started adjuvant chemotherapy and those that did not (median RFS 29.2 vs. 41.1 months,  $p = 0.819$ ; Supplemental Fig. 4c), but the RFS of those who received adjuvant chemotherapy for over 6 months was significantly better than that of those who received less than 6 months' treatment (median RFS 43.5 vs. 22.5 months,  $p = 0.016$ ; Supplemental Fig. 4d). The median duration of adjuvant therapy of those who received over 6 months in matched cohort was 10.1 months (6.2–64.4). The OS of patients who received adjuvant chemotherapy for over 6 months was also significantly better than that of those who received less than 6 months' treatment (median OS not reached vs. 48.2 months,  $p < 0.001$ ).

Cox proportional hazards regression analysis of RFS was performed to evaluate the prognostic importance of adjuvant chemotherapy. Univariate analysis identified ASA (American Society of Anesthesiologists) classification,

**Table 2** Incidence, 5-year survival rate, and calculated therapeutic benefit index for lymph node dissection in advanced non-ampullary duodenal cancer

Nodal station	Frequency of lymph node metastasis (%)			5-year survival rate of patients with metastatic nodes (%)			Therapeutic benefit index <sup>a</sup>		
	I ( $n = 136$ )	II ( $n = 366$ )	III/IV ( $n = 97$ )	I	II	III/IV	I	II	III/IV
No. 5	14.0	6.9	9.5	Censored	42.9	Censored	NA	3.0	NA
No. 6	34.8	10.3	0	47.0	0	-	16.4	0	NA
No. 7	15.8	8.3	0	0	0	-	0	0	NA
No. 8	33.6	11.1	2.3	29.0	18.8	0	9.8	2.1	0
No. 9	20.6	8.3	0	Censored	0	-	NA	0	NA
No. 12	24.2	13.6	2.2	57.4	29.6	0	13.9	4.0	0
No. 13	47.3	48.5	30.8	48.1	36.0	0	22.8	17.5	0
No. 14	28.8	24.8	28.8	58.2	31.1	11.7	16.8	7.7	3.4
No. 17	45.5	35.4	18.8	33.1	33.0	0	15.1	11.7	0
No. 16	3.2	14.4	16.7	0	22.4	27.8	0	3.2	2.4

I the first segment of the duodenum, II the second segment of the duodenum, III/IV the third/fourth segments of the duodenum, NA not applicable

<sup>a</sup>An index of the benefit gained by dissection at each station was calculated by multiplying the frequency of metastasis at that station by the 5-year overall survival rate of patients with metastasis at that station. The index was not determined for stations that had not been dissected in all patients or in which no metastasis was found after dissection. Likewise, we did not determine the index when all surviving patients with metastasis at that station had been censored within a 5-year period

**Table 3** Clinicopathological characteristics of the overall and one-to-one matched cohorts

	Overall cohort ( <i>n</i> = 1083)		<i>p</i> value	Matched cohort ( <i>n</i> = 376)		<i>p</i> value
	Adjuvant chemotherapy initiated ( <i>n</i> = 278)	Not initiated ( <i>n</i> = 805)		Adjuvant chemotherapy initiated ( <i>n</i> = 188)	Not initiated ( <i>n</i> = 188)	
Age, years	65 (32–84)	67 (19–90)	< 0.001	68 (32–84)	67 (19–90)	0.649
Sex			0.499			0.232
Female	97 (35)	263 (33)		70 (37)	59 (31)	
Male	181 (65)	542 (67)		118 (63)	129 (69)	
BMI, kg/m <sup>2</sup>	22.0 (13.3–34.2)	22.3 (12.3–40.9)	0.567	22.0 (13.3–31.2)	22.6 (13.0–33.8)	0.714
ASA classification			0.043			0.704
1–2	260 (94)	716 (89)		174 (93)	172 (91)	
≥ 3	18 (6)	85 (11)		14 (7)	16 (9)	
Tumor location			0.006			0.875
First segment	70 (25)	173 (21)		42 (22)	38 (20)	
Second segment	156 (56)	533 (66)		118 (63)	122 (65)	
Third/Fourth segments	52 (19)	99 (12)		28 (15)	28 (15)	
CEA, U/mL	2.6 (0.4–285)	2.5 (0.2–44.2)	0.635	2.8 (0.4–285)	2.8 (0.5–44)	0.838
CA19-9, U/mL	28 (1–67,700)	10 (1–20,780)	< 0.001	21 (1–3230)	13 (1–20,780)	0.102
Surgical procedure			< 0.001			0.973
Pancreatoduodenectomy	247 (89)	481 (60)	< 0.001	168 (89)	169 (90)	
Partial resection	19 (7)	259 (32)		10 (5)	9 (5)	
Distal gastrectomy	12 (4)	65 (8)		10 (5)	10 (5)	
Lymph node dissection	267 (96)	556 (69)	< 0.001	184 (98)	183 (97)	0.736
Tumor size, mm	40 (5–162)	30 (1–120)	< 0.001	40 (5–162)	40 (10–120)	0.907
Tumor depth			< 0.001			0.573
is/M	4 (1)	394 (49)		3 (2)	1 (1)	
SM	4 (1)	82 (10)		4 (2)	5 (3)	
MP/SS/SE/SI	270 (98)	329 (41)		181 (96)	182 (96)	
Positive lymph node metastasis	208 (76)	173 (26)	< 0.001	130 (69)	130 (69)	1.000
Histological differentiation type <sup>a</sup>			< 0.001			0.901
Differentiated	218 (79)	722 (90)		147 (78)	146 (78)	
Undifferentiated	59 (21)	81 (10)		41 (22)	42 (22)	
Residual tumor <sup>b</sup>			< 0.001			1.000
R0	249 (91)	775 (97)		176 (94)	176 (94)	
R1	25 (9)	24 (3)		12 (6)	12 (6)	

Data are expressed as median (range) for continuous variables and number (percentage) for categorical variables

*BMI* body mass index (calculated as weight in kilograms divided by height in metres squared), *ASA* American Society of Anesthesiologists, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19–9, *is/M* tumor in situ or confined to the lamina propria, *SM* tumor confined to the submucosa, *MP* tumor invades the muscularis propria, *SS* tumor invades the subserosa, *SE* tumor invasion is contiguous to the serosa or penetrates the serosa and is exposed to the peritoneal cavity, *SI* tumor invades adjacent structure

<sup>a</sup>Missing value in overall cohort: 3

<sup>b</sup>Missing value in overall cohort: 10

CEA (carcinoembryonic antigen), CA19-9 (carbohydrate antigen 19–9), tumor size, positive lymph node metastasis, pathological differentiation type, microscopically positive margin (R1), initiation of adjuvant chemotherapy, and over

6 months of adjuvant chemotherapy as significant predictors of RFS in the entire cohort (Table 4). Among these, CA19-9, positive lymph node metastasis, R1 status, and over 6 months of adjuvant chemotherapy were

independently associated with RFS. Furthermore, adjuvant chemotherapy for over 6 months was independently associated with prolonged RFS in the matched cohort [HR, 0.610; 95% confidence interval (CI), 0.437–0.839;  $p = 0.002$ ].

Finally, the efficacy of adjuvant chemotherapy in patient subgroups was analyzed. Adjuvant chemotherapy for over 6 months led to significant improvement in RFS in patients with SS or deeper tumors (HR, 0.626; 95% CI, 0.446–0.865;  $p = 0.004$ ), lymph node metastases (HR, 0.553; 95% CI, 0.377–0.793;  $p = 0.001$ ), and elevated CA19-9 levels (HR, 0.535; 95% CI, 0.331–0.838,  $p = 0.006$ ) (Fig. 3).

## Discussion

The rarity of non-ampullary duodenal cancers makes randomized clinical trials that could answer questions regarding diagnosis and optimal treatment challenging. Therefore, treatment strategy is often decided based on individual experience or institutional policy. To improve patient care, we conducted a nationwide survey and collected precise large-scale clinical data from accredited surgical centers in Japan. This study involving 1083 patients that underwent resection of non-ampullary duodenal cancer revealed several important findings.

The 5-year OS in the present study was 70.8%, more favorable than that reported previously [12, 13, 23–27]. This may be because our cohort included 484 patients with relatively early-stage tumors (is/M and SM), accounting for 44.7% of all patients. This is likely because esophagogastroduodenoscopy is a common practice in Japan due to the high incidence of gastric cancer. Furthermore, our study demonstrated that postoperative prognosis depends on tumor depth, suggesting that the optimal treatment may vary according to the depth of invasion, similar to other gastrointestinal cancers.

This study showed that the frequency of lymph node metastasis in each nodal station differed according to the tumor location. Therefore, the optimal surgical procedure for non-ampullary duodenal cancer would depend on the tumor location, depth of invasion, and extent of lymph node involvement.

Patients with is/M tumors are generally considered to have minimal risk of lymph node metastasis. In this study, 1.5% (6/398) of patients with is/M tumors had positive lymph nodes. Therefore, if precise pretreatment determination of tumor depth can be made, the optimal treatment for is/M tumors would be endoscopic resection. If endoscopic resection is not suitable or technically challenging, LR without lymph node dissection may be indicated. For SM tumors, curative-intent surgery with regional lymph

node dissection, mostly PD, may be generally recommended because lymph node metastasis is identified in > 10% of patients. However, pre- and intraoperative assessments of tumor depth and lymph node metastasis are occasionally unreliable, and over- or underestimations may occur. Therefore, if the final pathological examination after endoscopic resection or LR reveals a tumor depth of SM or deeper, a second surgery with lymph node dissection should be considered.

Regarding MP or deeper tumors, we demonstrated the pattern of spread for each nos. according to tumor location. We also determined the benefits of nodal dissection by evaluating the incidence of metastasis at each station and the corresponding 5-year survival rate, irrespective of metastases to other stations. The distribution of lymph node metastasis and therapeutic benefit of nodal dissection for tumors predominantly in the first and second segments were mostly similar. Therefore, PD may be oncologically adequate in these cases. While occasionally performed, DG for tumors predominantly located in the first segment may be insufficient because the metastasis rates and therapeutic value of dissection of the pancreatic nodes and those along the superior mesenteric artery were equivalent to those of infra-pyloric nodes and those along the common hepatic artery. In contrast, PD may be generally recommended for the complete removal of possible lymph node metastasis in third/fourth segment tumors. Pancreatic lymph nodes and those along the superior mesenteric artery are reasonable targets for dissection given the incidence of metastasis, although the apparent therapeutic benefit of dissection of tumors predominantly located in the third/fourth segments seems to be low. In nos. 6, 8, and 12, the rate of metastasis might be underestimated, as the frequency of dissection was very low. The clinical importance of PD is related to local control of the disease as well as comprehensive lymph node staging.

Para-aortic lymph node metastasis is currently considered as distant metastasis in almost all gastrointestinal malignancies. The therapeutic benefit index of para-aortic lymph node dissection was extremely low (0–3.2 in advanced tumors; Table 2). Thus, prophylactic dissection or aggressive resection is not recommended for patients with suspected para-aortic node metastasis. Taken together, this study suggested that PD could be the standard procedure for all cases of advanced non-ampullary duodenal cancer. Further, LR and DG may be tentatively recommended as an alternative option, especially for patients unable to tolerate PD.

The importance and optimal indications of adjuvant chemotherapy for non-ampullary duodenal cancer have not been established. In this study, approximately 25% of patients received adjuvant chemotherapy, mostly for advanced tumors. Since prospective randomized trials to



**Table 4** Univariate and multivariate analyses of predictive factors of recurrence-free survival

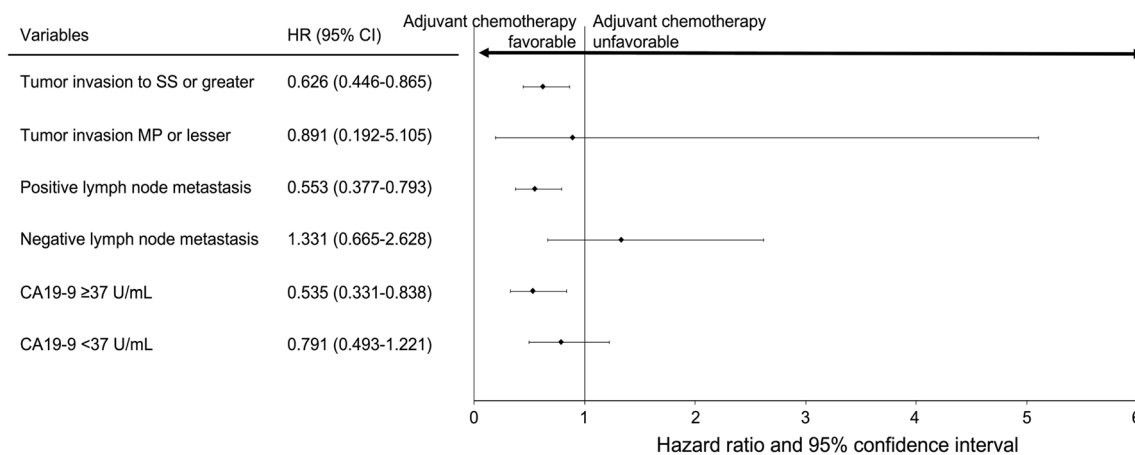
	Overall cohort (n = 1083)			Matched cohort (n = 376)		
	Univariate		Multivariate <sup>a</sup>	Univariate		Multivariate
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
ASA ≥ 3	1.912 (1.349–2.637)	< 0.001	1.398 (0.953–1.995)	0.085	1.847 (1.094–2.925)	0.023
CEA > 5.0 U/ml	2.019 (1.527–2.626)	< 0.001	1.168 (0.864–1.557)	0.306	1.462 (1.041–2.018)	0.029
CA19-9 > 37 U/ml	4.904 (3.879–6.198)	< 0.001	2.414 (1.861–3.133)	< 0.001	2.607 (1.946–3.495)	< 0.001
Tumor size, ≥ 50 mm	1.532 (1.190–1.957)	0.001	1.088 (0.831–1.412)	0.536	0.969 (0.708–1.315)	0.846
Positive lymph node metastasis	7.609 (5.804–10.109)	< 0.001	5.874 (4.328–8.058)	< 0.001	2.891 (2.016–4.269)	< 0.001
Differentiation type, undifferentiated	1.717 (1.259–2.297)	< 0.001	1.008 (0.721–1.380)	0.960	0.917 (0.628–1.306)	0.642
Residual tumor, R1	4.218 (2.845–6.033)	< 0.001	2.614 (1.709–3.869)	< 0.001	2.542 (1.483–4.072)	0.001
Initiation of adjuvant chemotherapy	3.438 (2.729–4.331)	< 0.001	NA	NA	0.967 (0.723–1.295)	0.820
Adjuvant chemotherapy > 6 months	1.923 (1.478–2.476)	< 0.001	0.659 (0.492–0.875)	0.004	0.677 (0.487–0.927)	0.014

HR hazard ratio, CI confidence interval, ASA American Society of Anesthesiologists, CEA carcinoembryonic antigen, CA19-9 carbohydrate antigen 19-9, NA not applicable

<sup>a</sup>Adjusted adjuvant chemotherapy > 6 months

explore the survival impact of adjuvant chemotherapy are not feasible in non-ampullary duodenal cancer, propensity score matching was utilized to minimize imbalances in patient demographics, tumors, and treatment-related covariates. Recently, two analyses from the National Cancer Data Base evaluating the efficacy of adjuvant chemotherapy in non-ampullary duodenal cancer were reported [28, 29]. One compared surgery alone with adjuvant chemotherapy for duodenal adenocarcinoma as a part of small bowel adenocarcinoma. In the matched cohort, OS was significantly improved with adjuvant chemotherapy in stage III tumors of the duodenum and jejunioileum [28]. The other showed that the addition of radiation to adjuvant chemotherapy had no survival benefit, even in high-risk patients with duodenal adenocarcinoma including positive-margin surgical resection and T4 classification [29]. Although the National Cancer Data Base is the authoritative registry of cancer statistics in the United States, it has some unavoidable limitations including the lack of detailed information of the adjuvant chemotherapy and long-term surveillance. We focused on clinical data collected over a decade at accredited high-volume surgical centers to ensure the reliability of data. Although previous reports had investigated OS, we evaluated RFS to clarify the true effect of adjuvant chemotherapy, as post-recurrence treatment affects OS. Adjuvant chemotherapy showed no survival benefit in the overall cohort. This was considered to be a product of selection bias, as adjuvant chemotherapy was administered for the more advanced tumors. The propensity-matched analysis demonstrated improved RFS when adjuvant chemotherapy was administered for > 6 months. Multivariate analysis indicated the favorable impact of administration for > 6 months. The exploratory subgroup analysis identified specific populations, including patients with SS or deeper tumors, positive lymph node metastasis, and preoperative elevated CA19-9 level, expected to benefit from adjuvant chemotherapy. Based on the data, > 6 months of adjuvant chemotherapy may be recommended for high-risk groups; however, the optimal regimen has not yet been established. The results from BALLAD (NCT02502370) and J-BALLAD (JCOG1502C) [30], ongoing open-label randomized controlled trials aiming to evaluate the benefit of three adjuvant chemotherapy regimens (infusional 5-FU/LV, FOLFOX, and capecitabine plus oxaliplatin) for resected small bowel adenocarcinoma, might help answer this question.

Our recommendations provide a tentative standard for non-ampullary duodenal cancer treatment. Nevertheless, this study had certain limitations. First, the study's retrospective nature meant that selection bias, including differing treatment strategies at each institution, is inevitable. In fact, the actual rate of regional lymph node metastasis remains unclear, as sufficient dissection might not have



**Fig. 3** Forest plot showing subgroup analysis of factors associated with recurrence after surgery. *HR* hazard ratio, *CI* confidence interval, *SS* tumor invades the subserosa, *MP* tumor invades the muscularis propria, *CA19-9* carbohydrate antigen 19-9

been performed in certain cases. Second, the small number of patients meant that we could not evaluate neoadjuvant therapy, which is an important topic in contemporary cancer treatment. Third, the therapeutic efficacy of radiation for non-ampullary duodenal cancer was not evaluated because its use is less common in Japan than in western countries [31]. However, the large-scale data presented in this study may provide useful information when managing this rare disease in daily clinical practice.

In conclusion, this study suggests that PD should be the standard procedure for advanced tumors. Furthermore, adjuvant chemotherapy for > 6 months appears to significantly improve survival. Further multi-institutional investigations are necessary to verify these recommendations.

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**Author contributions** All authors equally took part in the conception of the study. KN drafted the manuscript. MS supervised the writing of the manuscript. All authors approved the final version of the manuscript and unanimously agreed to be accountable for all aspects of the work and to ensure that any questions related to the accuracy or integrity of any part of the report are appropriately investigated and resolved.

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#### Declarations

**Conflict of interest** The authors have no conflicts of interest to disclose.

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