Received: 22 February 2021 | Revised: 3 March 2021 | Accepted: 30 March 2021
DOI: 10.1002/jhbp.956

ORIGINAL ARTICLE

Survey of surgical resections for neuroendocrine liver metastases: A project study of the Japan Neuroendocrine Tumor Society (JNETS)

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Abstract

Background/Purpose: Hepatic resection is considered the treatment of choice for neuroendocrine liver metastases (NELM). However, the safety and efficacy of resection have not been fully evaluated using a large cohort. The aim of the present study was to collect real-world data regarding hepatic resections for NELM.

Methods: A retrospective, multicenter survey was conducted. The background characteristics of patients undergoing an initial hepatic resection for NELM, the operative details, pathological findings, and patient outcomes were investigated.

Results: A total of 222 patients were enrolled from 30 institutions. The primary tumor site was the pancreas in 58.6%, and the presentation of NELM was synchronous in 63.1% of the cases. Concomitant resection of the primary tumor and liver metastases was performed for 66.4% of the synchronous metastases, and the 90-day morbidity and mortality rates were 12.6% and 0.9%, respectively. The operations resulted in R2

resections in 26.1% of the cases, and 83.4% of the patients experienced recurrence after R0/1 resections. However, the patients were treated using multiple modalities after R2 resection or recurrence, and the overall survival rate was relatively favorable, with 5-year and 10-year survival rates of 70.2%, and 43.4%, respectively. Univariable and multivariable analyses identified the tumor grading (G3) of the primary tumor as a significant prognostic factor for both the recurrence-free and overall survivals.
Conclusions: The present data confirmed the safety of the surgical resection of NELM. Although recurrences were frequent, the survival outcomes after resection were favorable when a multi-disciplinary treatment approach was used.

KEYWORDS

neuroendocrine liver metastasis, overall survival, postoperative complication, surgery, tumor recurrence

1 | INTRODUCTION

Neuroendocrine neoplasms (NENs) are rare neoplasms that include a wide spectrum of disease sites and histological subgroups. The incidence of NENs has reportedly increased during the last decade.[1,2] The current WHO classification[3,4] first stratifies NEN into well-differentiated NEN (NET) and poorly differentiated NEN (NEC); then, NET is sub-grouped into G1, G2, and G3 according to the Ki-67 index, and recent epidemiologic data from the United States has documented striking increases in localized-stage NENs as well as NET G1.[2] In contrast to the aggressive behavior of NEC, NET reportedly follows a relatively indolent clinical course; however, some NET tumors are found with distant metastases, especially liver metastases, at their presentation, and more than half of NET cases reportedly develop liver metastases during their clinical course.[5] The presence of liver metastasis adversely affects patient outcomes; thus, the management of liver metastases is of prime importance in the treatment of NEN patients.[6]

At present, surgical resection is the treatment of choice for neuroendocrine liver metastasis (NELM) whenever feasible, since patient outcomes after surgical resection have been reported to be favorable compared with those with unresectable tumors.[6,7] However, clinical trials comparing surgical resection and other treatment modalities are lacking, and real-world data surrounding NELM remains scarce. In the present study, we conducted a nationwide survey in Japan and collected clinical information regarding surgical resection to clarify the status of treatment for NELM.

2 | METHODS

2.1 | Study design

This retrospective, multicenter survey was planned as a project of the Japanese Neuroendocrine Tumor Society (JNETS). This study was conducted with the approval of the ethical committee of the JNETS as well as of Dokkyo Medical University Hospital (registration number: 27111) and each participating institution. Questionnaires were sent to the participating institutions, and the replies were collected and analyzed at the Second Department of Surgery, Dokkyo Medical University. The data collection was performed from June to September 2017.

2.2 | Patients

Patients undergoing an initial hepatic resection for NELM between January 2000 and June 2017 were enrolled in the present study. The collected data included background patient characteristics (age, sex, date of diagnosis, background disease [sporadic or hereditary], primary tumor site, functionality of the tumor, presentation of liver metastasis [synchronous or metachronous], and treatments prior to the liver resection), operative details (order of the operation [primary first, liver first, concomitant resection], extent of liver resection, tumor number, maximum tumor size, and radicality of the operation [R0, R1, or R2]), pathological results (differentiation of the primary tumor, grading of the primary tumor, differentiation of liver metastasis, grading of liver metastasis, and Ki-67 index of the primary tumor and liver metastasis), and surgical outcomes (90-day morbidity and mortality rates, presence of recurrence, recurrence-free survival [RFS] period after liver resection, treatments after R2 resection or recurrence, and overall survival [OS] period after liver resection). Postoperative complications classified as Clavien-Dindo grade 3 or more were recorded as morbidities.[8]

2.3 | Statistical analysis

The Ki-67 index of the primary tumor and liver metastasis were compared using the Wilcoxon signed-rank test.

Univariable and multivariable analyses were performed to investigate the significant clinicopathological factors associated with recurrence-free and overall survivals. The survival curves were generated using the Kaplan-Meier method. The analyses were conducted using SPSS version 25.0 (SPSS Inc) and BellCurve for Excel (Social Survey Research Information Co., Ltd.). Differences with $P < .05$ were considered as being significant.

3 | RESULTS

Thirty institutions participated in the present study, and a total of 222 patients were enrolled in the analyses. The names of the participating institutions are listed in Appendix S1.

3.1 | Background patient characteristics

Patient age ranged from 22 to 84 years (median, 56.0 years) at the diagnosis of NEN and from 22 to 84 years (median, 59.0 years) at the time of the first hepatic resection (Table 1). Nine patients had hereditary diseases; five had multiple endocrine neoplasia type 1, three had Von Hippel-Lindau disease, and one had Li-Fraumeni syndrome. The dominant primary tumor site was the pancreas in 130 (58.6%) patients, followed by the rectum in 28 (12.6%), the duodenum in 19 (8.6%), and the small intestine in 10 (4.5%). The primary tumor was functional in 29 cases. The presentation of liver metastasis was synchronous in 140 cases (63.1%) and metachronous in 82 cases (36.9%). Treatment prior to hepatic resection was performed in 51 patients (23.0%); somatostatin analogue therapy was performed in 15, molecular-targeting therapy was performed in 13, chemotherapy was performed in 21, and transcatheter arterial chemoembolization (TACE) was performed in 16. The number of modalities used before hepatic resection ranged from one to four.

3.2 | Operative procedures and short-term outcomes

Concomitant resection of the primary tumor and liver metastases was performed in 93 cases (66.4%) (Table 2), and the pancreas was the dominant concomitantly resected organ (n = 67). The pancreatectomy procedure consisted of a distal pancreatectomy in 49 patients, a pancreaticoduodenectomy in 16 patients, and a total pancreatectomy in two patients. In the other 47 patients, a liver first (n = 27) or a primary first (n = 20) approach was selected. The hepatic resection procedure consisted of a partial resection in 115 (51.8%) patients, a hemi-hepatectomy or more in 51 (23.0%), a segmentectomy in 33 (14.9%), and a sub-segmentectomy in 19 (8.6%). As a result, an anatomical resection was performed in 103 cases (46.4%). The number of resected tumors was one in 53 (24.1%) cases, 2-3 in 50 (22.7%), 4-10 in 58 (26.4%), and 11

TABLE 1 Clinical characteristics of the enrolled patients (n = 222)

Variable	Data
Age at the diagnosis of NEN, y, median (range)	56.0 (22-84)
Age at the hepatic resection, y, median (range)	59.0 (22-84)
Sex, male/female	113/109
Hereditary disease, yes/no	9/213
MEN type1, n	5
VHL, n	3
Li-Fraumeni syndrome, n	1
Primary site, n (%)	
Pancreas, n	130 (58.6)
Rectum, n	28 (12.6)
Duodenum, n	19 (8.6)
Small intestine, n	10 (4.5)
Stomach, n	9 (4.1)
Lung/bronchus, n	8 (3.6)
Bile duct, n	3 (1.4)
Colon, n	2 (0.9)
Others, n	13 (5.9)
Functional tumour, yes/no	29/193
Pancreas, n	26
Rectum, n	1
Small intestine, n	1
Stomach, n	1
Presentation of liver metastasis, n (%)	
Synchronous	140 (63.1)
Metachronous	82 (36.9)
Treatments prior to hepatic resection, yes/no	51/171
Somatostatin analogue, n	15
Molecular-targeting agents, n	13
Chemotherapy, n	21
TACE, n	16
RFA, n	5
Radiation, n	1
Number of treatment modalities performed prior to hepatic resection, n	
1	30
2	14
3	6
4	1

Abbreviations: N/A, not assessed; NEN, neuroendocrine neoplasm; RFA, radiofrequency ablation; TACE, transcatheter arterial chemembolization; VHL, Von Hippel-Lindau disease.

TABLE 2 Surgery-related variables

Variable	Data
Time-sequence of the resection of the liver and the primary in patients with synchronous metastasis, n (%)	
Concomitant resection	93 (66.4)
Liver first	27 (19.3)
Primary first	20 (14.3)
The organ(s) concomitantly resected with the liver, n	
Pancreas (PD/DP/TP)	67 (16/49/2)
Stomach/duodenum	9
Small intestine	8
Colon/rectum	4
Others	4
Procedure of hepatic resection, n (%)	
Partial resection	115 (51.8)
Hemi-hepatectomy or more	51 (23.0)
Segmentectomy	33 (14.9)
Sub-segmentectomy	19 (8.6)
N/A	4 (1.8)
Tumor number, n (%)	
1	53 (24.1)
2-3	50 (22.7)
4-10	58 (26.4)
11-20	20 (9.1)
21-	39 (17.7)
Maximum tumor size, cm, median (range)	3.0 (0.2-35.0)
Radicality of the operation, n (%)	
R0	140 (63.1)
R1	21 (9.5)
R2	58 (26.1)
N/A	3 (1.4)
90-day morbidity (Clavien-Dindo grade 3 or more), yes/no/unknown	28 (12.6)/191 (86.0)/3 (1.4)
90-day mortality, yes/ no/ unknown (n, %)	2 (0.9)/ 217 (97.7)/3 (1.4)

Abbreviations: DP, distal pancreatectomy; N/A, not assessed; PD, pancreaticoduodenectomy; TP, total pancreatectomy.

or more in 59 (26.8%), with a median size of 3.0 cm among the largest tumors. The operation was cytoreductive (non-curative) in 58 (26.1%) patients. The 90-day morbidity and mortality rates were 12.6% and 0.9%, respectively.

3.3 | Pathological results

The differentiation of the primary tumor was well-differentiated in 177 (79.7%) cases, poorly differentiated in 12 (5.4%) cases, and unknown in 33 (14.9%) cases (Table 3).

TABLE 3 Pathological variables

Variable	Data
Differentiation of the primary tumor, n (%)	
Well differentiated	177 (79.7)
Poorly differentiated	12 (5.4)
N/A	33 (14.9)
Grading of the primary tumor (WHO2010), n (%)	
G1	28 (12.6)
G2	82 (36.9)
G3	14 (6.3)
N/A	98 (44.1)
Differentiation of the liver metastasis, n (%)	
Well differentiated	97 (43.7)
Poorly differentiated	12 (5.4)
N/A	113 (50.9)
Grading of the liver metastasis (WHO2010), n (%)	
G1	13 (5.9)
G2	56 (25.2)
G3	12 (5.4)
N/A	141 (63.5)

Abbreviation: N/A, not assessed.

The grading of the primary tumor based on the WHO 2010 classification[9] was G1 in 28 (12.6%) cases, G2 in 82 (36.9%) cases, G3 in 14 (6.3%) cases, and unknown in 98 (44.1%) cases. The differentiation of the liver metastases was well-differentiated in 97 (43.7%) cases, poorly differentiated in 12 (5.4%) cases, and unknown in 113 (50.9%) cases. The grading of the liver metastases was G1 in 13 (5.9%) cases, G2 in 56 (25.2%) cases, G3 in 12 (5.4%) cases, and unknown in 141 (63.5%) cases.

Information regarding the grading of both the primary tumor and the liver metastasis were available in 46 cases. The results showed that an up-grading from the primary tumor to the liver metastasis was found in seven cases (15.2%; G1→G2, six cases; G1→G3, one case) and down-grading was found in five cases (10.8%; G2→G1, two cases; G3→G2, three cases).

Among the seven cases with up-grading, the presentation of liver metastasis was synchronous in four cases and metachronous in three cases. Information regarding the actual Ki-67 index values were available in 46 cases. The difference between the Ki-67 index of the primary tumor and that of the liver metastasis was insignificant ($P = .63$).

3.4 | Recurrence-free and overall survivals

After a median follow-up period of 42 months (range, 0-274 months; mean, 54.0 months), tumor recurrence had occurred in 146 (83.4%) cases among the patients who received R0/1 resections (Tables 4 and 5). The median RFS period after hepatic resection was 14.0 months, and the 1-year, 3-year, and 5-year RFS rates were 54.7%, 23.9%, and 13.4%, respectively (Figure 1A). The recurrence site was intra-hepatic only in 90 (63.4%) cases, extra-hepatic only in 11 (7.7%) cases, and both intra-hepatic and extra-hepatic in 40 (28.2%) cases. Treatments for residual tumors after R2 resection or recurrent tumors were conducted in 175 cases (91.1%) and included various modalities such as repeat hepatic resection, somatostatin analogue therapy, and molecular-targeting therapy. The median OS period after hepatic resection was 113 months, and 1-year, 3-year, 5-year, and 10-year OS rates were 91.8%, 83.1%, 70.2%, and 43.4%, respectively (Figure 1B). The OS curves stratified by the status of radicality (R0 vs R1 vs R2) showed that R2 resection was associated with unfavorable patient outcomes (R0/1 vs R2: $P = .03$) (Figure 2).

Regarding the grading of the liver metastasis and the primary tumor, there were no significant differences in overall survivals among the three subgroups (same grading, up-grading, and down-grading, $P = .82$). No significant differences were found when the results were stratified by the grading of the primary tumor (Figure S1).

TABLE 4 Patient outcomes

Variable	Data
Tumor recurrence after R0/1 resection, yes/ no, n, (%)	146 (83.4)/ 29 (16.6)
Site of recurrence, n (%)	
Intra-hepatic only	90 (63.4)
Extra-hepatic only	11 (7.7)
Intra- and extra-hepatic	40 (28.2)
N/A	1 (0.7)
Treatment(s) after R2 resection or recurrence, yes/ no/ unknown, n (%)	175 (91.1) /14 (7.3)/ 3 (1.6)
Treatment modality after R2 resection or recurrence, yes/ no, n (%)	
Surgical resection	67 (38.3)/ 108 (61.7)
Somatostatin analogue	82 (46.9)/ 93 (53.1)
Everolimus	54 (30.9)/ 121 (69.1)
Sunitinib	30 (17.1)/ 145 (82.9)
Streptozocin	29 (16.6)/ 146 (83.4)
Platinum-based chemotherapy	13 (7.4)/ 162 (92.6)
IVR (including TACE)	53 (30.3)/ 122 (69.7)
Liver-directed local therapy (including RFA)	20 (11.4)/ 155 (88.6)
Radiation	19 (10.9)/ 156 (89.1)

Abbreviations: IVR, interventional radiology; N/A, not assessed; NEN, neuroendocrine neoplasm; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization.

Univariable and multivariable analyses revealed that a grade G3 primary tumor was significantly associated with the RFS, and patient age and a grade G3 primary tumor were significantly associated with the OS. Other variables, such as the primary tumor site, synchronous presentation (Figure S2), and tumor number and size, were not identified as significant factors.

4 | DISCUSSION

In the present study, the authors conducted a nationwide survey of patients receiving surgical resections for NELM and enrolled 222 cases from 30 institutions. To our knowledge, this is one of the largest cohort studies examining surgical resection for NELM.

The epidemiology of NEN differs widely between Asian and Western countries. Previous Japanese survey data have documented that the dominant primary sites of gastroentero-pancreatic NEN were the pancreas and the rectum;[10] meanwhile, the incidence of NEN originating from the midgut is relatively low in Asian countries, compared with that in Western countries. In addition, the malignant potential of NEN also differs widely according to the primary site, and the pancreas and the rectum are stratified into the intermediate and unfavorable strata, respectively, while the small intestine is stratified into the favorable stratum.[2,11] Reflecting these epidemiological and biological backgrounds, the pancreas and the rectum were the dominant primary tumor sites in the present cohort. The results of the background characteristics also revealed that non-functioning tumors were predominant in this series, and two-thirds of the patients had synchronous liver metastases at the time of their presentation. As a result, only one-third of the patients received non-surgical treatments, including somatostatin analogue therapy and preoperative TACE, prior to hepatic resection; in other words, most of the patients in this study received up-front surgery.

A remarkable finding of this study was that the primary tumor and liver metastases were often resected concomitantly. In particular, a pancreatectomy with multiple partial resections of the liver was frequently performed. Furthermore, the morbidity and mortality rates were minimal. The surgical risk of combined pancreatectomy and hepatectomy procedures has been previously discussed[12,13]; the present results, however, showed that the concomitant resection of both the primary pancreatic tumor and liver metastases are justifiable. In addition, the survival outcomes were similar between synchronous and metachronous liver metastases (Figure S2). The result also supports this aggressive surgical approach.

On the other hand, up-front surgery resulted in R2 resections in 26.1% of the cases, and R2 resection was associated

TABLE 5 Univariable and multivariable analyses for (A) recurrence-free survival and (B) overall survival

Variables	N (%)	Univariable Analysis			Multivariable Analysis		
		Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
(A) Recurrence-free survival							
Age, ≥ 60	79 (35.6)	1.178	0.600-1.201	0.354			
Sex, male	113 (50.9)	0.873	0.620-1.233	0.44			
Functional tumor, yes	29 (13.1)	0.948	0.571-1.494	0.826			
Presentation of liver metastasis, metachronous	82 (36.9)	1.333	0.939-1.884	0.107			
Primary site, pancreas	129 (58.1)	1.02	0.722-1.451	0.911			
Grading, G3	14 (86.3)	2.477	1.064-5.093	0.037	2.449	1.052-5.040	0.039
Tumor number, ≥10	58 (26.1)	1.975	1.276-2.964	0.003	1.662	0.914-2.863	0.093
Maximum tumor size, ≥5cm	70 (31.5)	1.147	0.788-1.643	0.467			
Anatomical resection, no	150 (67.6)	0.964	0.677-1.389	0.84			
(B) Overall survival							
Age, ≥ 60	79 (35.6)	1.941	1.227-3.085	0.005	2.024	1.036-3.982	0.039
Sex, male	113 (50.9)	1.392	0.872-2.267	0.167			
Functional tumor, yes	29 (13.1)	1.231	0.669-2.127	0.486			
Presentation of liver metastasis, metachronous	82 (36.9)	1.107	0.691-1.751	0.669			
Primary site, pancreas	129 (58.1)	0.716	0.451-1.138	0.158			
Grading, G3	14 (86.3)	3.892	1.623-8.405	0.004	4.172	1.720-9.165	0.003
Tumor number, ≥10	58 (26.1)	1.044	0.588-1.757	0.877			
Maximum tumor size, ≥5cm	70 (31.5)	1.538	0.953-2.442	0.077			
R2 resection, yes	58 (26.1)	1.77	1.013-2.967	0.045	1.557	0.701-3.224	0.264
Anatomical resection, no	150 (67.6)	1.556	0.941-2.673	0.086			

with an unfavorable OS in a univariable analysis, although it was not identified as a significant prognostic factor in a multivariable analysis. Other previous reports have addressed the impact of cytoreductive surgery on patient outcome, and a consensus has not yet been reached.[6,14-17] The present findings suggest a need for neoadjuvant or conversion therapy for multiple NELM, and the significance of preoperative treatments should be clarified in future clinical trials.

After R0/1 resection, 83.4% of the patients experienced recurrence during the follow-up period and most of the patients developed intra-hepatic recurrence. The high recurrence rate found in this study was similar to the results of previous reports from Western series,[18,19] although the distribution of the primary tumor site in our series differed from that in the Western series. On the other hand, even after R2 resection or recurrence, 91.1% of the patients received additional treatments including repeat resection, somatostatin analogue therapy, molecular-targeting therapy, chemotherapy, and/or liver-directed local treatments. These results confirmed that NELM should be treated using a multi-disciplinary approach, and surgical resection can play a role, if performed in a timely manner, in this multidisciplinary strategy. In fact, the long-term outcomes of this study cohort were favorable, with 5-year and 10-year survival rates of 70.2% and 43.4%, respectively. Therefore, timely introduction of surgical intervention may be an optimal strategy in the relatively long treatment courses of NEN patients.

Recently, the significance of repeat resection for recurrent NELM has been reported.[19,20] Repeat hepatectomy, if feasible, can be a good option for intra-hepatic recurrence and can provide long-term survival. Therefore, the treatment policy for recurrences should be decided on a case-by-case basis and

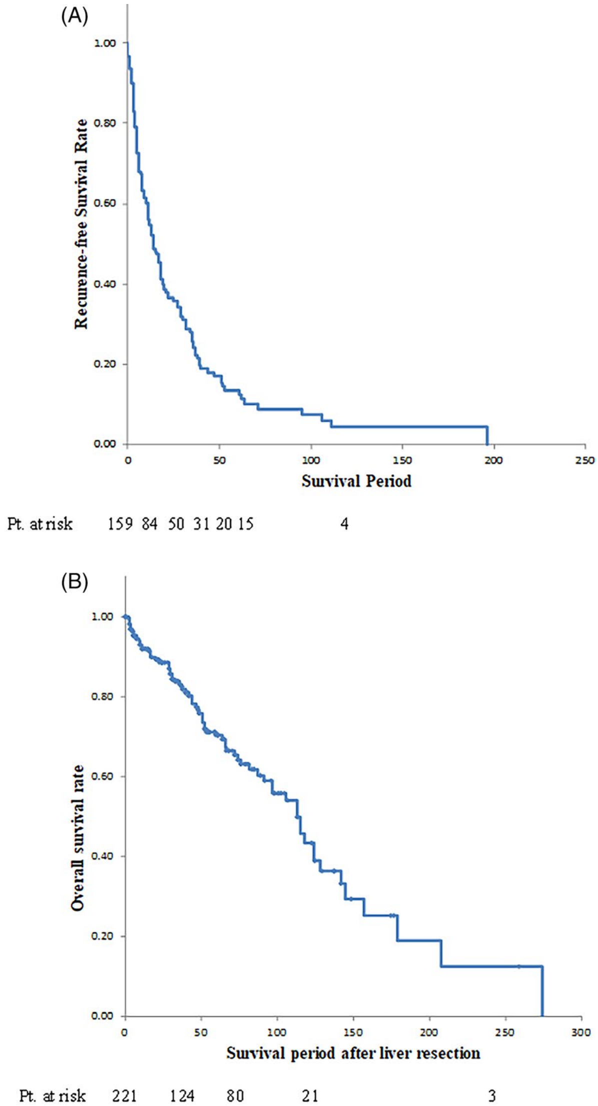


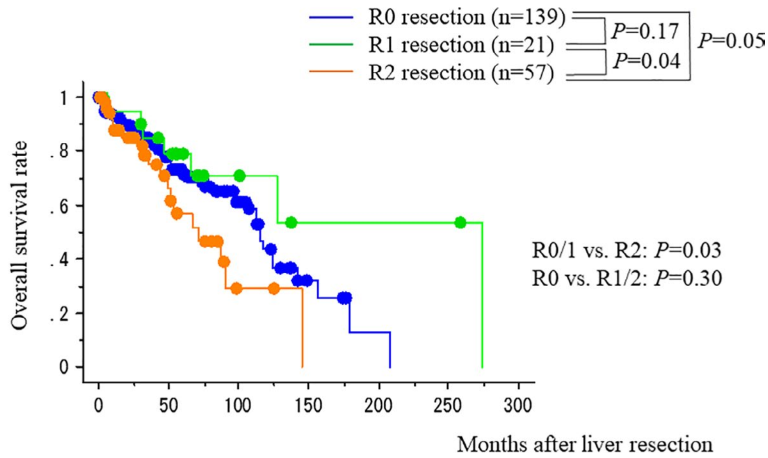
FIGURE 1 (A) Recurrence-free survival (RFS) curve after hepatic resection. The 1-year, 3-year, and 5-year RFS rates were 54.7%, 23.9%, and 13.4%, respectively. (B) Overall survival (OS) curve after hepatic resection. The 1-year, 3-year, 5-year, and 10-year OS rates were 91.8%, 83.1%, 70.2%, and 43.4%, respectively

should be a product of discussions among oncologists, gastroenterologists, and surgeons.

Multivariable analyses revealed that a G3 primary tumor was significantly associated with a short RFS and OS. In this series, G3 primary tumors included both well-differentiated NET (NET G3 in the WHO 2017 classification) and poorly differentiated NEC, and the two categories cannot be discussed separately. In any case, the surgical indications for liver resection should be cautiously determined for NELMs with high Ki-67 index values. On the other hand, other variables including the primary tumor site, tumor number, tumor size, and R2 resection were not identified as being significant in multivariable analyses, although these factors have been reported as prognostic factors in previous reports.[5-7,21-24] These results may be attributable to a bias in the cohort, such as the fact that the primary tumor site was the pancreas in more than half of the tumors and that about half of the patients underwent multiple partial hepatic resections for relatively small tumors. Nevertheless, R2 resections, especially for G3 tumors, are not good indications for surgical resection, and therefore, cytoreductive surgery should be attempted as a part of a multi-disciplinary treatment approach.

The present results showed that up-grading and down-grading between the primary tumor and the liver metastasis sometimes occurred (15.2% and 10.8%, respectively), although only 46 pairs of specimens could be assessed in this series. Of note, this phenomenon was found in cases with both synchronous and metachronous metastases. Recent reports have documented that up-grading from the primary tumor to liver metastases, as well as heterogeneity among the liver metastases, are frequently found, and these reports have recommended a re-evaluation of the Ki-67 index prior to the start of anti-tumor treatments for tumor progreesion.[25-27] Our results may support their recommendations, and the Ki-67 index should be evaluated for both the primary site and the metastatic site. Previous reports suggested that the survival outcomes were favorable in patients with a lower Ki-67 index in the metastases than the primary tumor when compared with the patients with a higher Ki-67 index in the metastases than the primary tumor, and up-grading of the Ki-67 index in the metastases was more frequently observed when the disease became progressive.[26,27] On the other hand, there was no significant difference in overall survival among the three subgroups of same grading, up-grading, and down-grading in the present analyses (Figure S1). These conflicting results may be ascribed to the small number of patients in each group, and as a result, a definite conclusion cannot be drawn. Further investigation is needed to clarify the significance of up- and down-grading of the liver metastasis.

This study had several limitations. First, detailed information about the clinical course of each patient was not available because of the nature of the survey data. Therefore, the efficacy of each treatment modality could not be assessed. Second, the examinations of pathological variables were insufficient, as information regarding tumor differentiation, tumor grading, and the actual Ki-67 index value were only available for a limited number of patients. The current WHO classification recommends that a description of the actual Ki-67 index value be included on pathological reports; if more sophisticated information becomes available in the near future, researchers will be able to discuss interesting topics, such as NELM grade migration from that of the primary tumor and a comparison of NET G3 and NEC.



Pt at risk

R0 resection	139	55	14	0
R1 resection	21	11	4	2
R2 resection	57	11	2	0

FIGURE 2 Overall survival (OS) curves stratified by the radicality of the operation (R0 vs R1 vs R2). R2 resection was associated with an unfavorable OS

ACKNOWLEDGEMENTS

The authors thank all the colleagues who participated in this survey project. The context of this study was presented at the 13th IHPBA World Congress 2018, Geneva, Switzerland.

CONFLICTS OF INTEREST

We have no conflicts of interest to declare.

AUTHORS' CONTRIBUTIONS

TA and KK conceived the study. TA searched the published literature. JA, CM, TM, AK, IK, EH, TI, RYO, MU, and NK are members of the Committee on Treatment of NEN Liver Metastasis of JNETS. TA and KK performed the data analyses and interpreted the data. TA and KS performed the statistical analyses. TA wrote the first draft of the report. All the authors approved the final version of the report.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Aoki T, Kubota K, Kiritani S, et al. Survey of surgical resections for neuroendocrine liver metastases: A project study of the Japan Neuroendocrine Tumor Society (JNETS). *J Hepatobiliary Pancreat Sci*. 2021;28:489–497. https://doi.org/10.1002/jhbp.956