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Surgical resection of neuroendocrine tumor liver metastases as part of multimodal treatment strategies: A propensity score matching analysis

Teresa Schreckenbach [a,*], Helga Hübert [a], Christine Koch [b], Jörg Bojunga [b], Andreas A. Schnitzbauer [a], Wolf O. Bechstein [a], Katharina Holzer [c]

[a] Frankfurt University Hospital, Goethe University Frankfurt/Main, Department of General- and Visceral Surgery, Frankfurt am Main, Germany
[b] Frankfurt University Hospital, Goethe University Frankfurt/Main, 1st Department of Internal Medicine, Gastroenterology and Hepatology, Frankfurt am Main, Germany
[c] Marburg University and Clinics, Department of General- and Visceral Surgery, Section of Endocrine Surgery, Marburg, Germany

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ABSTRACT

Background: It remains unclear whether liver resection as part of multimodal therapy of neuroendocrine liver metastases (NELM) is superior to non-surgical (interventional and medication-based) treatment alone. This study should determine if patients with NELM undergoing hepatic surgery in addition to non-surgical treatment have improved overall survival compared to patients undergoing non-surgical therapy alone.
Methods: 123 patients undergoing treatment of NELM between 1995 and 2014 were included in this retrospective cohort study. Two groups were formed: (A) surgery and non-surgical therapy and (B) non-surgical treatment alone. To minimize the bias of patient selection propensity score matching was used.
Results: There was significantly better overall survival for group A (152 months, 95%CI: 119–185) compared to group B (63 months, 95%CI: 45–81) measured from the initial diagnosis of the metastases (P = 0.003). After propensity score matching, 37 patients undergoing surgical resection of NELM within a multimodal treatment were compared to 37 patients undergoing non-surgical treatment. Under these circumstances, surgery had no significant influence on survival (group A: 134 months, 95% CI: 94–173; group B: 76 months, 95% CI: 53–99, P = 0.23). Based on a multivariate Cox proportional hazard model, only Ki-67 of primary tumor >20% (HR, 50.776; 95%CI, 4.056–635.71; P = 0.002) and no resection of primary tumor (HR, 10.464; 95%CI, 1.873–58.448; P = 0.007) remained independent risk factors.
Conclusion: After minimizing patient selection bias, patients with hepatic resection as integral of multimodal therapy of NELM do not have better overall survival than those receiving non-surgical treatment alone.

Introduction

A high percentage of neuroendocrine neoplasms (NENs) are known for their slow and benign progression, but at least 40% of patients with NEN develop liver metastases [1]. In patients with untreated neuroendocrine liver metastases (NELM), the overall 5-year survival is 24–52% [2–4]. NELM represents a special challenge for multimodal therapeutic strategies including medication-based therapy, surgery, interventional treatment, and peptide receptor radionuclide therapy (PRRT) [5–7]. Nevertheless surgical resection of NELM or liver transplantation remains the only curative therapy option for patients [8,9].

To date, there is no clear evidence for the benefit of surgery in patients with NELM [10]. Also, there is a lack of randomized clinical trials comparing patients, who undergo multimodal treatment with and without surgical resection. There are studies showing a survival benefit for patients undergoing surgical resection [11,12],

* Corresponding author. Frankfurt University Hospital Goethe University Frankfurt/Main Department of General and Visceral Surgery, Theodor-Stern-Kai 7, 60590, Frankfurt/Main, Germany.
E-mail address: Teresa.Schreckenbach@kgu.de (T. Schreckenbach).

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but studies for interventional-based treatments have also shown a good 5-year survival rate [13–16]. Our study aimed to compare patients undergoing NELM surgical resection in the context of multimodal treatment strategies with patients receiving only non-surgical multimodal therapy. To achieve better comparability between the two groups, propensity score matching was performed.

Methods

This retrospective study was performed at a single center. No ethical concerns were raised by the Ethics Committee of the Goethe University, Frankfurt, Germany (Registration number 76/15).

Patients

This study included all patients who were treated for NELM at the University Hospital Frankfurt between May 1995 and December 2014. Using a retrospective institutional database, 123 patients with NELM were identified. Patients were categorized based on their treatment approach: (1) Group A underwent surgical treatment (n = 47) and non-surgical treatment, and (2) Group B underwent only non-surgical therapies (n = 76) without surgery.

Analyzed variables and baseline definitions

Standard demographic and clinicopathologic data were collected, including sex, age, body mass index (BMI), and comorbidities. Comorbidities were scored using the Charlson Comorbidity Index [17].

For primary tumor characteristics, date of diagnosis, tumor localization, tumor grading, Ki-67, the presence of symptoms, and date of surgery for removal of the primary tumor were collected. NELM data included number, localization, time of presentation, and clinical symptoms and Ki-67 as an index for proliferation. For patients undergoing surgery, surgical data were also collected, including the extent of surgery, duration of surgery, and postoperative complications. Hepatic resection included patients who had undergone right or left hemihepatectomy, trisectorectomy, left lateral resection, and wedge resection. Postoperative complications were scored according to the Clavien-Dindo classification as no complication or complication grades I to V [18].

Non-surgical therapies included interventional treatment and medication-based therapy. For interventional treatment, transarterial chemoembolization (TACE), radiofrequency ablation (RFA), laser-induced thermotherapy (LITT), and selective internal radiation therapy (SIRT) and PRRT were identified.

Medication-based therapy included: (1) somatostatin analogs; (2) interferon; (3) chemotherapies; and (4) biological-target therapies. Patients undergoing chemotherapy received streptozotocin, gemcitabine, 5-fluorouracil, doxorubicin, temozolomide, capecitabine, cisplatin, carboplatin or etoposide. Biological-target therapies included treatment with sunitinib, everolimus or bevacizumab.

Study endpoints

The primary endpoint of the study was overall survival. The secondary endpoint was 10-year mortality measured from the baseline. The baseline for follow-up was the date of NELM diagnosis. The end of follow-up was the date of death or, if not available, the date of the last follow-up.

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows (version 22.0; IBM, Chicago, IL). Categorical variables were described in frequencies and percentages. Continuous variables were represented as the median and its range. Categorical variables were compared using the χ^2-test or Fisher's exact test, as appropriate. Continuous variables were compared using the Student's *t*-test. Overall Survival (OS) was estimated using a Kaplan-Meier survival analysis considering the time-to-event in months. Survival curves were generated using the Kaplan-Meier method and differences in survival were tested using the log-rank test.

A propensity score matching was performed to reduce the patient selection bias. Propensity score matching was performed with R version 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria) using the package 'Matching' [19]. Covariates used to calculate the propensity index were based upon previously published studies [20–22]. The parameters used for matching were age, localization of primary tumor, primary tumor grading, resection of primary tumor, number of liver metastases, extrahepatic tumor manifestations, and Charlson Comorbidity Index. Propensity score matching was added to the uni- and multivariate Cox regression model.

Factors potentially associated with 10-year mortality were analyzed using the Cox proportional hazard model with stepwise selection. A univariate Cox proportional hazard model analysis was performed with all variables and those with a P-value < 0.05 were used for multivariable analysis.

Parameters included in the multivariate analysis after propensity score matching were Ki-67 of the primary tumor and primary tumor resection. To avoid multicollinearity, unknown primary tumor localizations, as well as those in the small bowl, were not included, even if significant in the univariate analysis. P-values < 0.05 were considered statistically significant. Results were expressed as a hazard ratio [23] with a 95% confidence interval (CI).

Results

Overall patient and primary tumor characteristics

For baseline characteristics, only the percentage of primary tumor resections differed significantly between Groups A and B (80.9% vs. 48.6%, respectively; $P < 0.005$; Table 1).

Medication-based treatment in the unmatched groups

Twenty-three patients (48.9%) in Group A received somatostatin analog therapy, compared with 41 patients (53.9%) in Group B ($P = 0.59$). One patient (2.1%) in Group A and three patients (4.1%) in Group B received interferon ($P = 0.49$). In Group A, 15 patients (31.9%) underwent different types of chemotherapy compared with 29 patients (39.7%) in Group B ($P = 0.39$). Four patients in Group A (8.5%) and five patients (6.8%) in Group B received a biological-targeted therapy ($P = 0.72$).

Interventional treatment in the unmatched groups

In Group A, eight patients (17.0%) underwent TACE, and one patient (2.1%) underwent RFA. In Group B, 28 patients (36.8%) underwent TACE, and two (2.6%) patients underwent RFA. There was no significant difference between the groups ($P = 0.07$).

Overall, 11 patients underwent a second interventional treatment. In Group A, one patient (2.1%) received RFA, and one patient (2.1%) received LITT. In Group B, one patient (1.3%) underwent TACE, one (1.3%) underwent RFA, one underwent LITT (1.3%), and one (1.3%) underwent SIRT. There was no significant difference between the groups ($P = 0.63$).

Table 1
Baseline characteristics of the study and control groups before propensity score matching.

	Total (%) (n = 123)	Group A (%) (n = 47)	Group B (%) (n = 76)	Pearson Chi-Square (df)	P-value
Sex				2.5 (1)	0.14
male	66 (53.7)	21 (44.7)	45 (59.2)		
ASA-Score				1.5 (3)	0.68
3	15 (2.2)	11 (37.9)	4 (25.0)		
Primary NEN localization				7.6 (7)	0.37
Stomach	4 (3.3)	1 (2.1)	3 (3.9)		
Pancreas	41 (33.3)	15 (31.9)	26 (34.2)		
Small bowel	36 (29.3)	19 (40.4)	17 (22.4)		
Appendix	1 (0.8)	1 (2.1)	0		
Colon	4 (3.3)	1 (2.1)	3 (3.9)		
Rectum	3 (2.4)	1 (2.1)	2 (2.6)		
Other	9 (7.3)	2 (4.3)	7 (9.2)		
Unknown	25 (0.3)	7 (14.9)	18 (23.7)		
Ki-67 primary tumor (n = 86)				0.6 (2)	0.73
<2%	28 (22.8)	12 (34.3)	16 (31.4)		
2–20%	45 (36.6)	19 (54.3)	26 (51.0)		
>20%	13 (10.6)	4 (11.4)	9 (17.6)		
Primary tumor resected				15.3 (2)	**<0.005**
yes	74 (61.2)	38 (80.9)	36 (48.6)		
Metachronous presentation	35 (28.5	13 (30.2)	22 (31.9)	0.3 (1)	0.51
Presence of symptoms	39 (31.7)	15 (34.9)	24 (36.4)	0.1 (1)	0.52
Presence of extrahepatic disease	77 (62.9)	32 (68.1)	45 (60.8)	0.7 (1)	0.45
Metastases Ki-67 (n = 64)				0.6 (2)	0.74
<2%	7 (5.7)	4 (13.3)	3 (8.8)		
2–20%	42 (34.1)	20 (66.7)	22 (64.7)		
>20%	15 (12.2)	6 (20.0)	9 (26.5)		
Localization of NELM				3.4 (3)	0.34
bilateral	85 (69.1)	35 (76.1)	50 (76.9)		
Number of NELM				2.2 (3)	0.54
solitary	5 (4.1)	3 (6.7)	2 (3.0)		
up to 4	14 (11.4)	7 (15.6)	7 (10.6)		
diffuse	91 (74.0)	35 (77.8)	56 (84.8)		
	Total (n = 123)	Group A (n = 47)	Group B (n = 76)	F- ratio	P-value
Age in years (mean, SD)	57 (13)	55 (14)	58 (11)	1.6	0.22
Charlson Comorbidity Index, (mean, SD)	7 (1)	7 (1)	7 (1)	0.4	0.52

NELM, neuroendocrine liver metastases, ASA, American Society of Anesthesiologists, NEN, Neuroendocrine Neoplasm.

Peptide receptor radionuclide therapy (PRRT) in unmatched groups

Six patients (12.7%) in Group A and four patients (5.3%) in Group B were treated with PRRT as the first interventional treatment. Two patients of Group A received PRRT (4.3%), and three patients of Group B received PRRT (4.0%) as a second interventional treatment. There were no significant differences between the groups (P = 0.40).

Propensity score-matched patient and primary tumor characteristics

After propensity score matching, there were no significant differences between the groups among the baseline characteristics (Table 2).

Medication-based treatment in the matched groups

Eighteen patients (48.6%) in Group A and 21 patients (58.8%) in Group B received somatostatin analog therapy (P = 0.49). One patient (2.7%) in Group A and two (5.4%) in Group B received interferon during therapy (P = 0.56). In Group A, 11 patients (29.7%) underwent different types of chemotherapy, compared with 12 patients (33.3%) in Group B (P = 0.74). Four patients in Group A (10.8%) and three (8.1%) in Group B received a biological-targeted therapy (P = 0.69).

Interventional treatment in the matched groups

30 (41.9%) patients received additional interventional treatment. In Group A, seven patients (23.3%) underwent TACE, and one patient (3.3%) underwent RFA. In Group B, 14 patients (46.7%) underwent TACE, and two patients underwent (6.7%) RFA. There was no significant difference between Groups A and B (P = 0.09).

Overall, eight patients underwent a second interventional treatment. In Group A, one patient (3.3%) received RFA, one patient received PRRT (3.3%), and one patient (3.3%) received LITT. In Group B, one patient (3.1%) underwent TACE, and one underwent LITT (3.3%). There was no significant difference between the groups (P = 0.53).

Peptide receptor radionuclide therapy (PRRT) in matched groups

Five patients (16.7%) in Group A and one patient (3.3%) in Group B were treated with PRRT as first interventional treatment. One patient (3.3%) in Group A, and two patients (6.6%) in Group B received PRRT as a second interventional treatment. There were no significant differences between the groups (P = 0.86).

Surgery characteristics in the matched surgery group (Group A)

Thirteen patients (38.2%) underwent minor resections; 20 patients (54.0%) underwent major resections; three patients (8.1%) underwent liver transplantation. In one patient resection extent

Table 2
Baseline characteristics of the study and control groups after propensity score matching.

	Total (%) (n = 74)	Group A (%) (n = 37)	Group B (%) (n = 37)	Pearsons Chi-Square (df)	P-value
Gender				2.7 (1)	0.10
male	43 (58.1)	18 (48.6)	25 (67.6)		
ASA-Score (n = 32)				1.5 (3)	0.67
3	11 (34.4)	8 (33.3)	3 (37.5)		
Primary NEN localization				1.9 (5)	0.86
Stomach	2 (2.7)	1 (2.7)	1 (2.7)		
Pancreas	17 (23.0)	10 (27.0)	7 (18.9)		
Small bowel	30 (40.5)	16 (43.2)	14 (37.8)		
Rectum	3 (4.1)	1 (2.7)	2 (5.4)		
Other	6 (8.1)	2 (5.4)	4 (10.8)		
Unknown	16 (21.6)	7 (18.9)	9 (24.3)		
Ki-67 Primary tumor (n = 55)				0.1 (2)	0.99
<2%	18 (32.7)	9 (33.3)	9 (32.1)		
2–20%	31 (56.4)	15 (55.6)	16 (57.1)		
>20%	6 (10.9)	3 (11.1)	3 (10.7)		
Primary tumor resected				0.3 (1)	0.59
yes	56 (75.7)	29 (78.4)	27 (73.0)		
Metachronous presentation (n = 69)	20 (29.0)	10 (28.6)	10 (29.4)	0.1 (1)	0.93
Presence of symptoms (n = 70)	26 (37.1)	12 (35.3)	14 (38.9)	0.1 (1)	0.76
Presence of extrahepatic disease	47 (63.5)	24 (64.9)	23 (62.2)	0.1 (1)	0.81
Metastases Ki-67 (n = 39)				0.2 (2)	0.89
<2%	5 (12.8)	3 (13.6)	2 (11.6)		
2–20%	24 (61.5)	14 (63.6)	10 (58.8)		
>20%	10 (25.6)	5 (22.7)	5 (29.4)		
Localization of NELM (n = 73)				4.6 (2)	0.09
bilateral	54 (74.0)	28 (75.7)	26 (72.2)		
Number of NELM				0.1 (2)	0.96
solitary	6 (8.1)	3 (8.1)	3 (8.1)		
up to 4	15 (20.3)	8 (21.6)	7 (18.9)		
diffuse	53 (71.6)	26 (70.3)	27 (73.0)		
	Total (n = 74)	Group A (n = 37)	Group B (n = 37)	F- ratio	P-value
Age in years, (mean, SD)	60 (11)	59 (12)	61 (10)	0.2	0.66
Charlson Comorbidity Index, (mean, SD)	7 (1)	7 (1)	7 (1)	0.2	0.67

NELM, neuroendocrine liver metastases, ASA, American Society of Anesthesiologists, NEN, Neuroendocrine Neoplasm.

could not be classified retrospectively. Twenty patients (54.0%) received a wedge resection, left lateral resection, and/or non-anatomic resections; six patients (16.2%) received a right hemihepatectomy; two patients (5.4%) received a left hemihepatectomy; six patients (16.2%) underwent planned debulking surgery. R0 resection was achieved in 18 patients (48.6%), and the pathological report showed an R1 resection in five patients (13.5%) and an R2 resection in nine patients (24.3%). In five patients (13.5%), no information about resection status was available retrospectively.

No postoperative complications occurred in 13 (35.1%) patients. Grade I or II complications were diagnosed in six patients (16.2%), and grade III complications occurred in nine patients (24.3%). Three patients developed grade IV (8.1%) complications. Two patients died after surgery (5.4%), one because of lung embolism on the fourth postoperative day and one due to myocardial infarction on the first day after surgery. For four patients, no data about postoperative complications were available. The median duration of surgery was 240 min (range, 45–500 min). Nine patients (24.3%) in Group A underwent resection of the primary tumor during the same operation.

Comparison of survival with unmatched groups

The OS measured from the first NEN diagnosis in all patients was 213 months (95% CI: 169–259). The OS measured from diagnosis of liver metastases for all patients was 119 months (95% CI: 94–144). There was significantly better survival for Group A (152 months, 95%CI: 119–185) compared to Group B (63 months, 95%CI: 45–81) measured from the initial diagnosis of the metastases (P = 0.003; Fig. 1).

Comparison of survival between groups after propensity score matching

The OS measured from the first NEN diagnosis for all 74 selected patients was 136 months (95% CI: 110–163). The OS measured from the NELM diagnosis for selected patients was 120 months (95% CI: 89–152). After propensity score matching, there was no significant survival difference between the groups (Group A: 134 months, 95% CI: 94–173; Group B: 76 months, 95% CI: 53–99, P = 0.23) measured from the initial diagnosis of metastases (Fig. 2).

Cox regression analysis of 10-year mortality in unmatched groups

The 10-year mortality for all patients was 20.3%. Based on the multivariate Cox proportional hazard model, Ki-67 of the primary tumor >20% (HR, 7.193; 95%CI, 1.314–39.37; P = 0.02) remained an independent risk factor. Presence of symptoms (HR, 0.108; 95%CI, 0.013–0.906; P = 0.04) remained as an independent protective factor (Table 3).

Cox regression analysis after propensity score matching for 10-year mortality

After propensity score matching, the 10-year mortality for selected patients was also 24.3%. Ki-67 index of primary tumor >20% (HR, 50.776; 95%CI, 4.056–635.71; P = 0.002) and no resection of primary tumor (HR, 10.464; 95%CI, 1.873–58.448; P = 0.007) were included in the multivariate Cox proportional hazard model.

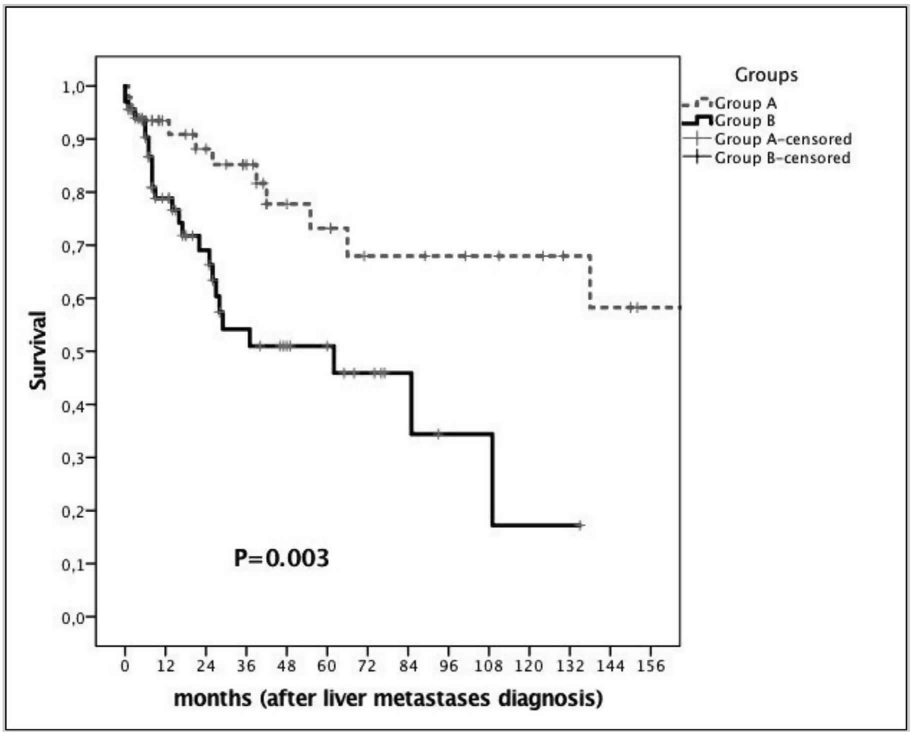

Fig. 1. Kaplan-Maier survival for unmatched groups of patients who did or did not undergo surgery.

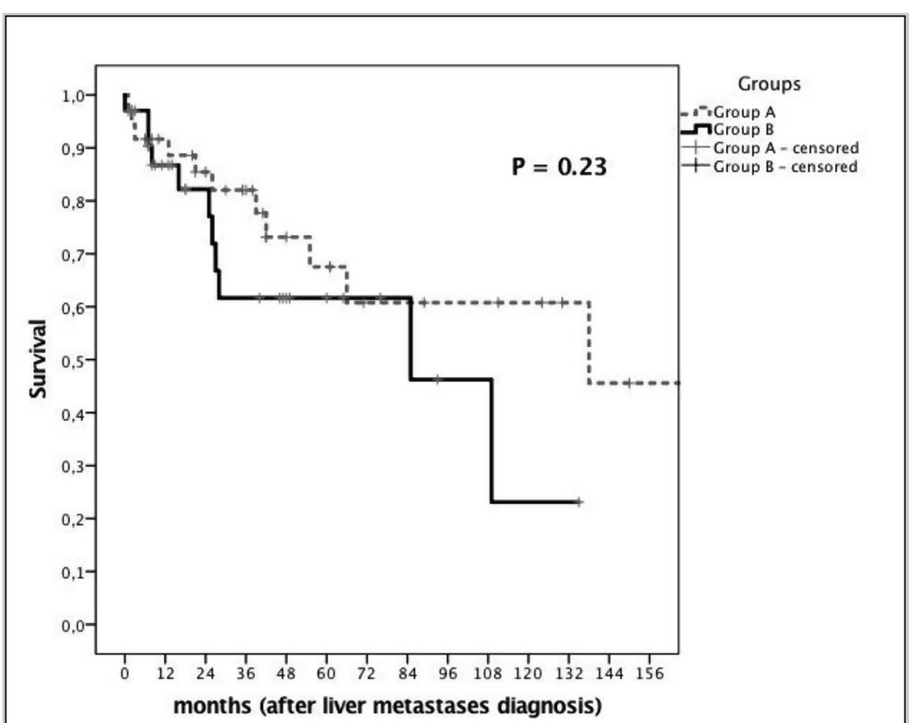

Fig. 2. Kaplan-Maier survival for matched groups of patients who did (Group A) or did not (Group B) undergo surgery.

Table 3
Cox proportional hazard model for factors influencing 10-year mortality before and after propensity score matching.

Factors	Before Matching (n = 123)						After Matching (n = 74)					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Age	1.026	0.992–1.060	0.136				1.037	0.992–1.084	0.110			
Sex												
male	1.454	0.659–3.210	0.354				0.801	0.325–1.974	0.629			
ASA												
ASA ≥ 3	0.658	0.119–3.636	0.631				5.889	0.657–52.79	0.113			
Primary tumor in Pancreas	0.918	0.395–2.136	0.843				0.730	0.241–2.213	0.578			
Primary tumor in the small bowel	0.309	0.090–1.062	0.062				0.275	0.091–0.831	**0.022**[a]	–	–	
Unknown primary tumor	2.240	0.922–5.441	0.075				4.066	1.561–10.592	**0.004**[a]	–	–	–
Ki-67 Primarius												
>20%	11.192	2.047–61.178	**0.005**	7.193	1.314–39.37	**0.023**	20.729	2.131–201.61	**0.009**	50.776	4.056–635.71	**0.002**
Primary tumor resected												
no	2.349	0.931–5.927	0.070				4.248	1.659–10.875	**0.003**	10.464	1.873–58.448	**0.007**
Metachronous presentation	0.649	0.260–1.620	0.354				0.678	0.239–1.922	0.465			
Presence of symptoms	0.085	0.019–0.384	**0.001**	0.108	0.013–0.906	**0.040**	0.446	0.155–1.284	0.135			
Presence of extrahepatic disease	0.808	0.350–1.866	0.617				0.918	0.360–2.344	0.858			
Ki-67 Metastases												
>20%	17.287	1.916–155.95	**0.011**				–	–	–			
Number of NELM												
diffuse	3.346	0.770–14.543	0.107				2.456	0.316–19.102	0.391			
Resection of metastases												
no	1.443	0.571–3.652	0.438				1.552	0.628–3.837	0.341			

NELM, neuroendocrine liver metastases, ASA, American Society of Anesthesiologists.
Bold text indicates a statistically significant difference with a P-value less than 0.05.
[a] Not included in the multivariate analysis to avoid multicollinearity.

Both factors remained independent risk factors. Details of the analysis are shown in Table 3.

Recurrence of intrahepatic tumor

In the unmatched surgery group, 18 patients (38.3%) developed recurrent intrahepatic metastases after surgical resection. The mean disease-free survival (DFS) was 42 months (SD, 13 months). Sixteen patients (43.2%) in the matched surgery group developed new liver metastases after hepatic resection. The mean DFS was 30 months (SD, 11 months). Twenty-one patients (56.8%) did not develop new NELM.

Discussion

Considering the high frequency of NELM, there is a lack of randomized studies that compare different treatment strategies, especially the influence of surgical resection within a multimodal treatment plan. Also, there are only a few studies that use a propensity score matching to ensure that the basic characteristics of the groups are not significantly different.

In a study by Norlén et al. using propensity score matching, no survival benefit could be shown for patients with NELM undergoing surgery and RFA compared to patients who only received non-surgical treatment [16]. These results demonstrate that the beneficial findings for liver surgery might be biased concerning the selection of patients with lower liver burden and comorbidities [7]. In our study, comparing the unmatched patients with and without liver surgery, we detected a significant survival benefit for the patients in the liver resection group.

In this study, the local and systemic therapies were mixed in the non-surgical treatment group in this study. RFA and TACE are interventional therapies, which aim for a local control of the metastases, as does surgical resection. As the study of Norlen et al. suggests, surgical treatment and RFA may be equivalent [16].

Since patients in the comparison group also received local treatment of metastases, this might account for the lack of survival differences between groups. Local non-surgical treatments for oligometastatic NEN, especially in patients with contraindications against surgical intervention might also give a good option for local tumor removal [24] and improve survival.

Looking more closely at these data, we note that those patients with liver resection have had their primary tumor removed significantly more often than patients in the non-surgical treatment group. After using propensity score matching, the survival advantage effect vanished. This result is consistent with studies that have shown that resection of the primary NEN tumor results in a significant improvement of survival prognosis. Citterio and coauthors reported significantly improved survival in patients with NELM undergoing resection of their primary tumor [21].

For rare tumors, propensity score matching is an important statistic tool for establishing correct relationships among the data. As Daskalakis et al. found for the prophylactic surgical approach to stage IV small-intestine NEN, the results in unmatched and matched groups can differ [25]. These authors found a significantly better survival for asymptomatic patients undergoing resection of stage IV small-intestine NEN. After using propensity score matching, no significant survival difference remained [25]. Also, for other questions related to the ideal therapy of NELM, propensity score matching was found to enable a sufficient analysis of the data [26,27]. Zhang et al. found that after matching their groups of synchronous and metachronous NELM, there was no survival difference between the groups [27].

Other authors have suggested that patients with a Ki-67 index >20% do not benefit from surgical resection. A high Ki-67 is a well-known risk factor for worse survival [28]. A study by Watzka et al. reported that patients undergoing liver resection due to NELM have a better prognosis if the Ki-67 index was less than 20% [3]. Performing a Cox proportional hazard analysis for all patients, we also showed that a Ki-67 > 20% in the primary tumor has a negative influence on 10-year OS. Even after propensity score matching, a Ki-67 index >20% remained as an independent risk factor for an increased 10-year mortality.

Thus, the benefits of NELM resection in patients with a high Ki-67 index should be critically evaluated. Frilling et al. have issued recommendations on how neuroendocrine liver metastases should be treated [24]. In their review, they show that patients with a low Ki-67 index benefit from follow-up care because, in case of disease recurrence, they often benefit from multimodal therapy. We suggest, that patients with a high Ki-67 index should be critically evaluated in an interdisciplinary tumor board, as they do not seem to benefit from surgical treatment and might be better treated with systemic therapy strategies.

Additionally, we found that the presence of hormone-related symptoms seems to have a protective influence in a Cox regression analysis for all patients. These results could be compared to other studies, which have reported that the presence of hormone-related symptoms is a positive factor for better 10-year survival [3]. However, after propensity score matching, we could not reproduce this finding in the multivariate Cox proportional hazard analysis. Sarmiento et al. had shown better clinical symptom control in patients undergoing hepatic resection [8]. When looking closer at this study, we noted that most of the included patients underwent liver resection, whereas alternative treatment strategies were rare [8]. Similar results were reported by Nave et al., but again these treatment strategies (especially in interventional and medication-based treatment) have developed since that time [29].

However, about 50% of patients with liver surgery as an integral part of multimodal therapy had a recurrence-free survival over the years, which is consistent with other studies [10,16].

These findings should be openly discussed with patients and referring physicians. In our opinion, surgery should be a part of a multimodal treatment strategy for patients with NELM, but not a single-choice treatment. Especially for oligometastatic patients with a low Ki-67 index, surgical resection of NELM is a chance for cure.

Limitations

This study has limitations, which are mostly due to its retrospective character. The included patient number is small and, after propensity score matching, resulted in even smaller samples of patients. With a larger number of patients, some results might have been significant. Also, a limitation of the study, especially for the unmatched groups, was the composition of the groups. Local and systematic treatment strategies were mixed in the non-surgical group. Local therapies, such as surgical resection, offer a local control of NELM. A differentiation between surgical, local and systemic therapies might lead to other results. Limitations could also result from the statistical methods that we used. For the Cox proportional hazard model, only parameters that were statistically significant in the univariate analysis were used for the multivariate analysis. It is possible that insignificant variables in the univariate analysis would have become significant in the multivariate analysis by using other methods of variable entry, such as forward or backward selection.

However, our data are representative of real clinical practice and have some important strengths. Since 2007, patients (72% of the included patients) were repeatedly represented in our NEN-Board, where physicians of different specialties, discussed their cases. This enabled reliable clinical information and a long observation period. Using propensity score matching avoided comparing groups differing significantly in baseline characteristics. Also, an important strength of this study is the distribution of the conservative treatment strategies between the groups. Patients' undergoing surgery also underwent medication-based and interventional therapy. There was no significant difference between the groups and surgery was one part of the multimodal treatment.

As the data suggest, the aim of the treatment strategy for patients with NELM should be a personalized therapy. To improve the opportunity for tailored therapy strategies more prospective randomized multicenter-studies comparing local and systemic treatments for NELM should be conducted.

Conclusion

In conclusion, surgical resection of NELM as part of a multimodal therapy strategy shows no significant improvement in survival compared with only non-surgical treatment strategies.

Despite this, surgery should always be considered for each patient with a Ki-67 index <20%, as there remains a possibility for a cure and control of clinical symptoms. A high percentage (56.8%) of the patients remained tumor free after multimodal treatment including surgery. For patients with a Ki-67 index >20% surgical therapy should be discussed very critically as they might not benefit from it.

Declarations

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Conflict of interest

The authors declare that they have no conflicts of interest.

Author contributions

All authors made substantial contributions to the design and analysis of this work, which included drafting and assessing the manuscript. All authors approved the final manuscript for submission and agreed to be accountable for the work.

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Abbreviations

ASA	American Society of Anesthesiologists
BMI	body mass index
DFS	disease free survival
LITT	laser-induced thermotherapy
NEN	neuroendocrine neoplasm
NELM	neuroendocrine liver metastases
OS	overall survival
PRRT	peptide receptor radionuclide therapy
RFA	radiofrequency ablation
SIRT	selective internal radiation therapy
TACE	transarterial chemoembolization

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