Selective internal radiation therapy for neuroendocrine liver metastases: efficacy, safety and prognostic factors. A retrospective single institution study

D. Briol*[5], A. Ceratti*[1], R. Lhommel[3] , L. Annet[2], C. Dragean[2], E. Danse[2], P. Trefois[2], M. Van Den Eynde[1], A. de Cuyper[1], P. Goffette[2], I. Borbath[4]

(1) Cliniques universitaires Saint-Luc (CUSL), Oncology, Brussels, Belgium; (2) Cliniques universitaires Saint-Luc (CUSL), Radiology, Brussels, Belgium; (3) Cliniques universitaires Saint-Luc (CUSL), Nuclear Medicine, Brussels, Belgium; (4) Cliniques universitaires Saint-Luc (CUSL), Gastroenterology, Brussels, Belgium; (5) CHU UCL Namur, Saint-Elisabeth, Oncology, Namur, Belgium.

Abstract

Background and study aims: **Selective internal radiation therapy (SIRT) has shown good results in unresectable liver metastases from neuroendocrine neoplasms (NELM) with a high disease control rate (DCR) reported. The aims of the study is to assess retrospectively the efficacy and safety of 10y of SIRT for NELM.**

Patients and methods: **Primary endpoint was objective response rate (ORR) and DCR by RECIST 1.1 at 2, 4 and 12 months (m). Secondary endpoints were overall survival (OS), liver progression-free survival (liver-PFS), clinical response (NEN-related symptoms improvement) and safety.**

Results: **50 consecutive patients with NELM who got SIRT from 2011 to 2021 in one center. The two major NEN primary sites were pancreas (46%) and small intestine (36%). Histological NEN grades were 10%, 46% and 44% for grades 1, 2 and 3 respectively. ORR and DCR were 16% and 80% at 2m, 22% and 92% at 4m and 32% and 82% at 12m. Survival rates at 1 and 2 y were 76% and 72% respectively. Prognostic factors for OS and liver-PFS were NEN histological grade (3 vs 1+2) (hazard ratio (HR) for OS: 4.33 [1.8-10.6], for liver-PFS: 3.91 [1.3-11.4]), and early (2m) DCR (HR for OS: 0.14 [0.1-0.4], for liver-PFS: 0.016 [0.003-0.08]). Clinical response occurred in 7 of the 10 symptomatic patients. One patient died from radioembolization-induced liver disease.**

Conclusion: **SIRT showed efficacy in NELM pts, with a high DCR and an good safety profile. G1-2 grade and early DCR were associated with a better OS and liver-PFS. (**Acta gastroenterol belg., **2025**, 88, **3-11**).

Keywords: SIRT, neuroendocrine tumours, effectiveness, outcomes, liver metastases.

Introduction

Neuroendocrine neoplasms (NENs) are a heterogeneous family of rare tumours of increasing worldwide incidence and concern (1,2). They can arise from foregut (lung, thymus, stomach, duodenum and pancreas), midgut (small intestine and proximal colon) and hindgut (distal colon, rectum) structures (3).

The diagnosis of NENs is based on clinics, histology, biomarkers and medical imaging (4). World Health Organization (WHO) classifies NENs as either well-differentiated neuroendocrine tumours (NETs), poorly differentiated neuroendocrine carcinomas (NECs) or mixed neuroendocrine-non neuroendocrine neoplasms (MiNENs) (5). Furthermore, NENs are graded as grade 1 (G1), grade 2 (G2) or grade 3 (G3) based on the Ki-67 index (cell proliferation marker, assessed by immunohistochemistry) (and/or mitotic index [number of mitosis per 10 high-power fields], seldom realized nowadays). NECs are high grade by definition (6,7). G1 tumours are defined by a Ki67 index < 3%, G2 tumours by a Ki67 index of 3 -20 % and G3 tumours have a Ki67 index > 20% (8).

More than half of NENs arise from the gastro-entero-pancreatic tract (GEP) (9). NENs can be functioning or non-functioning depending on the production and releasing of peptide hormones or biogenic amines by tumour cells (10). Functioning NENs are less common; for instance, functioning pancreatic NENs constitute about 20% of all pancreatic NENs (4,11).

A large cohort study based on data from the European Neuroendocrine Tumor Society (ENETS) registry has demonstrated that 47% of patients with NEN were metastatic at diagnosis, associated with a poorer survival prognosis (3,11,12).

Therapies include local treatment: surgery, percutaneous ablation, transarterial (chemo)embolization (TACE) and Selective internal radiation therapy (SIRT); or systemic: peptide receptor radiation therapy (PRRT), somatostatine analogues, chemotherapy and targeted therapies.

SIRT, also referred as transarterial radioembolization (TARE) is a minimally invasive therapy to treat liver malignant tumours, whether primary or metastatic. Radioactive isotope labelled microspheres are directly injected into the liver, through the hepatic artery. Primary (i.e. hepatocellular carcinoma (HCC)) and some type of secondary liver tumours are mainly vascularized by hepatic arterial vasculature, unlike the healthy liver parenchyma which is fed mainly by the portal vein (3,13). The more vascularized are the tumours, the more can microspheres be lodged in the tumor arterioles. Then, high-energy β-radiation is directly delivered to neoplastic cells (absorbed doses ranging from 100 to 1000 Gy (14)), while healthy liver tissue is relatively spared (15). Irradiation aims to induce tumour cell death thanks to apoptosis process and proliferative ability inhibition (14,16). On the

* Equitable contribution as first author.
Correspondence to: D. Briol : CHU UCL Namur site Sainte-Elisabeth, Service d'Oncologie, Place Louise Godin 15, 5000 Namur.
Email: damien.briol@chuuclnamur.uclouvain.be

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contrary, hypovascularized tumours escape treatment due to this preferential arterial flow and hepatotoxicity is higher due to the lack of arterioles selectivity. (3).

There are three types of commercially available microspheres, based on the embedded radioactive isotope and microsphere material (3,13): resin ^{90}Yttrium (^{90}Y) microspheres (SIR-Spheres, Sirtex Medical, Sydney, Australia), glass ^{90}Yttrium microspheres (TheraSpheres, Boston Scientific, Boston, USA) and poly-L-lactic acid ^{166}Holmium microspheres (QuiremSpheres, Quirem Medical B.V., Deventer, The Netherlands). These types differ by some characteristics, particularly size, density, activity per microsphere and embolic effect. SIRT has shown promising results in unresectable neuroendocrine neoplasm with liver metastasis (NELM) with a high disease control rate (DCR), as reported in a recent multi-center study (17). Several prognostic factors have been highlighted in this trial, such as NEN grade, intrahepatic tumour load ≥ 75%, extrahepatic disease and DCR; other data in the literature are not consistent with the prognostic factors, due to the heterogeneity of studies and their limited sample size (18,19).

The aim of this retrospective study was to assess the efficacy and safety of 10 years of SIRT for patients with unresectable NELM in our centre, and to look for prognostic factors of efficacy.

Methods

Patient eligibility

After approval from the local ethics committee (Comité d'Ethique Hospitalo-Facultaire Saint-Luc -UCLouvain), data from the Electronic Medical Record were retrieved. All selected patients underwent SIRT for NELM at *Cliniques Universitaires Saint Luc* (*Brussels*, Belgium), from October 2011 (first SIRT performed in the center for this indication) to June 2021. SIRT was proposed to patients with NEN of any origin, proven by histology and/or cytology, with progressive NELM that were deemed not suitable for radical treatments after discussion at the Multidisciplinary Team Discussion (MTD), previously treated or not. Consents have been obtained from each patient after full explanation of the purpose and nature of all procedures used. Extrahepatic disease (defined as extrahepatic NEN metastasis) was not contraindicated but needed to be stable and low volume disease (at the physicians discretion, concluded at MTD). Adequate hepatic, renal and hematological functions were needed (Hepatic function: adequate coagulation tests and total bilirubin < 2 mg/dL, renal function: glomerular filtration rate > 30 mL/min/1.73m², hematological function: not more than grade 2 cytopenia), as well as ability to undergo angiography and catheterization procedures.

A baseline and at least one 2 months post-treatment imaging by contrast-enhanced computed tomography (CT) or gadolinium-enhanced magnetic resonance imaging (MRI) were required, as well as a safety follow-up (clinical and biological). Liver metastatic disease had to Erreur !

Signet non défini.be measurable according to Response Criteria in Solid Tumors (RECIST) version 1.1 (20). Patients with ongoing systemic treatments were eligible for SIRT provided controlled extrahepatic disease.

Following data were collected at baseline: demographics, Eastern Cooperative Oncology Performance Score (ECOG PS), primary anatomical NEN site, ENETS/WHO tumour grade based on a histological/cytological specimen (if more than one specimen: worst grade was retained), Ki67 proliferation index, tumour differentiation, prior anti-neoplastic therapies, liver tumour load (defined as visual estimation as more or less than 75% of liver tissue), sites of extrahepatic metastases if present, presence of endocrine symptoms, laboratory parameters including complete blood cell count, liver function tests and tumour markers (chromogranin A, neuron-specific enolase and 5-hydroxyindolacetic acid).

SIRT procedure

SIRT required a multidisciplinary team composed by a radiologist, a nuclear medicine physician, an interventional radiologist and a NEN oncologist. The team discussed the indication, performs the dose calculation and treatment.

Unilobar or bilobar SIRT could be performed, based on tumour burden and location.

Sometimes, sequential treatment were performed for bilobar tumours.

SIRT was realized in two phases, each requiring a 1-2 day hospitalization: firstly, a "simulation" phase, to assess tumour vascularization, to limit the risks of toxicity during treatment as much as possible and to plan the optimal dose for the treatment. To do this, the Interventional radiologist performed a hepatic arteriography, then injected technetium-99m macroaggregates of albumin (MAA), a diagnostic radiopharmaceutical agent simulating the injection of radiolabeled-microspheres. Following MAA administration, a single photon emission computerized tomography (SPECT)-CT was performed in order to evaluate hepatic and extrahepatic uptake of MAA, allowing the nuclear medicine physician to assess uptake in healthy liver tissue, the absence of excessive uptake by the lungs (to assess the risk of radiation-induced pneumonitis) and abnormal uptake by gastrointestinal tract. So, this simulation determined if SIRT was an appropriate treatment option and allowed treatment dose adjustments. Ten to 14 days after the simulation phase, microspheres were infused by the interventional radiologist with the catheter positioned in the exact same location as during the simulation phase. Just after SIRT was completed, ^{90}Y positron emission tomography (PET)-CT was performed, allowing to depict the ^{90}Y micro-spheres distribution in the tumour and the liver.

Proton pump inhibitors (PPI) were prescribed to all patients during 4 to 6 weeks after SIRT as radiation-induced ulcer and gastritis prophylaxis. Prophylactic somatostatin analogs were administered only if patient suffered from secretory syndrome.

For the purpose of the study, the following data were collected: date of treatment, type of microspheres injected, use of anti-reflux micro-catheter, selective, lobar or bilobar injection, and activity administration (calculated as follow : Activity (GBq) = (Body Ssurface Area – 0.2) + Volumetumor/[Volumetumor + Volumenormal (targeted) liver].

Study outcome parameters

Primary endpoints were tumour objective response rate (ORR) and DCR according to RECIST 1.1, at 2, 4 and 12 months after SIRT. Secondary endpoints were overall survival (OS), liver progression-free survival (liver-PFS), clinical response (NEN related symptoms improvement) and safety. Correlation between tumour marker response (PR considered as decrease of at least one of tumour marker more than 50% after SIRT, PD considered as increase of more than 50%; SD if other cases) and radiological response was explored. Moreover, tumour marker values before and after SIRT were compared.

If the whole liver had to be treated in a two-stage sequential procedure, tumour imaging was performed after the second SIRT administration (with the same time points as non-sequential treatment). Liver-PFS was defined as the time from the first day of treatment to the date of progression, death or new treatment (local or systemic). These events were monitored during 12 months after SIRT (author's arbitrary decision). Liver-PFS for subjects without progression was censored after 12 months. ORR was defined as the sum of patients achieving a complete response (CR) or partial response (PR). DCR was defined as CR, PR + stable disease (SD). OS was defined as the time from the first day of treatment to death. OS of subjects alive at the time of analysis was censored at the last date known to be alive. Improvement of pretreatment NEN related symptoms was assessed at 2 months. Clinical and biological SIRT-related toxic effects were graded according to the *National Cancer Institute Common Toxicity Criteria for Adverse Events* (NCI-CTCAE), version 5.0. The worst grade of toxic effect per patient was recorded.

Tumour assessment was stopped for patients who had to receive a new treatment for extrahepatic disease progression or for any other cause to avoid bias on primary outcome.

Statistical analysis

Baseline descriptive statistics were summarized as median and range for continuous variables and as counts and proportions for categorical variables. Correlation between tumour marker response and radiological response was assessed with Spearman correlation coefficient. Wilcoxon's test was used to compare tumour marker values before and after SIRT. Survival analysis was calculated from the day of SIRT using the Kaplan–Meier method, and subgroup comparisons were per-formed using log-rank tests. A multivariate analysis of survival was performed with the use of a Cox proportional-hazard model to evaluate the SIRT effect with adjustment for prognostic factors, even if these variables were not significant in univariate analysis. Explored prognostic factors were NEN histological grade, early DCR, intrahepatic tumour load $\geq$ 75%, primary tumour site origin, primary tumour site surgery, extrahepatic disease and baseline bilirubin CTCAE $\geq$ 1.

Statistical analyses were done using R version 3.6.1. All p-values (p) were 2-tailed, and statistical significant level was set *a priori* at $p < 0.05$.

Results

Patient characteristics at baseline

A total of 51 patients with NELM were treated with SIRT between October 2011 and June 2021. At least one post-treatment tumour imaging assessment (CT or MRI), similar to the baseline one, was available for 50 patients. One patient was excluded from analysis, due to death not related to study disease or SIRT (unfortunately, the patient committed suicide).

Table 1 shows the baseline patients' characteristics. Median age was 63,4 (27,2-83,0) years and sex ratio (male/female) was 1.1. Baseline ECOG PS was 0 or 1 in 96% of patients. Major primary NEN sites were pancreas (46%) and small intestine (36%); extrahepatic disease was present in 46% of patients. Of note, 10 patients had poorly differentiated NEN (origin: 60 % pancreas, 20 % small intestine, 10 % common bile duct and 10 % lung). Histological grade was 3 in 22 patients (44%). Among these G3 NENs, 63% (14/22) were of pancreatic origin, 18.5% (4/22) of small intestine origin and 18.5% (4/22) of other origin. Extrahepatic metastases were present in 40% (9/22), including 45% (4/9) with lymph node and/or bone metastases. Median Ki67 was 26.3% (range 20-90%), indicative of probable good differentiation of the tumors, with 31% (7/22) of patients that had a ki67 greater than or equal to 50%.

Ten patients presented NEN related symptoms: 5 patients had flushing, 3 patients diarrhea, 1 patient concomitant flushing and diarrhea and 1 patient hypoglycemia.

Ninety-two percent of the cohort received at least 1 prior treatment for NELM (local or systemic treatment). More than half of the patients received somatostatine analogues as prior treatment. Only one patient underwent a second SIRT procedure following liver progression without extra hepatic disease. The second SIRT procedure was performed 3 months after the first one. The disease

Table 1

Baseline characteristics and previous treatment (N =50)	
	Median (range) or n (%)
Age (years)	63.4 (27.2-83.0)
Sex	
Male	27 (54)
Female	23 (46)
ECOG PS	
ECOG 0	27 (54)
ECOG 1	21 (42)
ECOG 2	1 (2)
ECOG 3	1 (2)
Primary NEN site	
Pancreas[1]	23 (46)
Stomach	1 (2)
Common bile duct	1 (2)
Small intestine[2]	18 (36)
Large intestine	2 (4)
Lung/bronchus	4 (8)
Unknown origin	1 (2)
Extrahepatic metastases	
No	27 (54)
Yes[3]	23 (46)
Presence of endocrine symptoms	
No	40 (80)
Yes	10 (20)
ENETS/WHO grade	
G1 (Ki67 index < 3 %)	5 (10)
G2 (Ki67 index 3-20 %)	23 (46)
G3 (Ki67 index > 20 %)	22 (44)
NEN differentiation	
Well	35 (70)
Poor	10 (20)
Unknown	5 (10)
Resected primary tumour	
No	17 (34)
Yes	33 (66)
Previous treatments for NENLM	
Naïve	4 (8)
One	18 (36)
Two	15 (30)
Three	7 (14)
Four or more	6 (12)
Previous systemic treatments	
Chemotherapy[4]	19 (38)
Targeted therapies[5]	22 (44)
Somatostatin analogues	29 (58)
Immunotherapy	1 (2)
Time from NEN diagnosis to SIRT (years)	2.15 (0.15-31.3)
Previous radionuclide treatments	
^{90}Y-PRRT	4 (8)
Previous liver-directed treatments	
TACE	2 (4)
PEI	2 (4)
Stereotactic radiotherapy	1 (2)
Previous liver-directed surgical treatments	
Segmentectomy	1 (2)
Left hepatectomy	2 (4)
Right hepatectomy	0 (0)
Ongoing treatments	
Somatostatin analogues	21 (42)
Others[6]	8 (16)

SIRT: Selective Intern Radiation Therapy, ECOG PS: Eastern Cooperative Oncology Performance Score, NEN: Neuroendocrine Neoplasm, ENETS: European Neuroendocrine Tumour Society, WHO: Word Health Organization, TACE: Transarterial chemo-embolization, PEI: Percutaneous Ethanol Injection, ^{90}Y-PRRT: ^{90}Yttrium-Peptide Radionuclide Receptor Therapy. [1]Functioning NEN: gastrinoma (2%), insulinoma (2%), VIPoma (2%). [2]Functioning NEN: somatostatinoma (2%). [3]Lymph nodes (30%), bone (18 %), peritoneum (10%), lungs (8 %), other (12%). [4]Cisplatine/etoposide (18%), carboplatin/etoposide (2%), streptozotocin/doxorubicin (2%), temozolomide (10%), temozolomide/capecitabine (10%), capecitabine (2%), FOLFIRI (5 Fluorouracil/folinic acid/irinotecan) (8%), FOLFOX (5 Fluorouracil/ folinic acid/ oxaliplatin) (2%), FOLFIRINOX (5 Fluorouracil/folinic acid/irinotecan/oxaliplatin) (2%). [5]evero-limus (24%), sunitinib (32%), bevacizumab (2%). [6]Temozolomide/capecitabine (6 %), temozolomide (2%), everolimus (4%), sunitinib (4%).

remained stable for one year following this second SIRT procedure. In both cases, the treatment was performed on the whole liver. The patient experienced no complication.

Table 2

Liver metastases and SIRT characteristics	
	n (%)
Type of microspheres administrated	
Resin ^{90}Yttrium microspheres (SIR-Spheres©)	40 (80)
Glass ^{90}Yttrium microspheres (TheraSpheres©)	10 (20)
Use of anti-reflux micro-catheter (Surefire© infusion system)	
No	28 (56)
Yes	22 (44)
Whole liver or single lobe treated	
Whole liver, single treatment	32 (64)
Whole liver, sequential treatment[1]	7 (14)
Right lobar	9 (18)
Left Lobar	2 (4)
Net administrated ^{90}Y activity (GBq) [2]	
Left unilobar, median (range)	1.70 (1.57-1.83)
Right unilobar, median (range)	1.94 (0.57-3.56)
Bilobar, median (range)	1.83 (0.7-6.06)

GBq : Gigabecquerel. [1] Median time from the first lobe treated to the second one was 63 days (range: 28 - 126 days).[2] Activity (GBq) = (BSA – 0.2) + $Volume_{tumour}$/[$Volume_{tumour}$ + $Volume_{normal\ (targeted)\ liver}$] BSA means Body Surface area (in m²).

Resin ^{90}Yttrium microspheres (SIR-Spheres) was the main type of microspheres administrated (80%) (Table 2). As the procedures progressed, the choice of SIRT team fell on SIR-Spheres Whole liver treatment occurred in 78% (64% single treatment and 14% sequential treatment).

Clinical and biological SIRT-related Toxicities

All patients were assessable for safety during the one-year post-treatment follow-up. Table 3 summarizes all adverse events (AE) probably or possibly related to SIRT, split by grading. Toxicity of any grade occurred in 44 patients (88%). Thirty-five patients (70%) presented grade 1-2 AE, which included abdominal pain (n=12, 24%), lymphocytopenia (n=13, 26%), liver cytolysis (defined as Alanine/ Aspartate aminotransferase increase) (n=16, 32%), cholestasis (n=12, 24%). Nine patients (18%) presented grade 3-4 AE: lymphocytopenia (n=6, 12%) and cholestasis (n=3, 6%).

One patient died from radioembolization-induced liver disease (REILD) (grade 5 AE).

There were no statistical differences in side-effects between SIR-Spheres and TheraSpheres .

Response rate

Fifty, 36 and 28 Patients were assessed for the 2, 4 and 12 months follow-up time points respectively, as they were shown to be controlled by SIRT, and not treated by a subsequent therapy (table 4). ORR and DCR were 16% (8/50) and 80% (40/50) at 2 months (defined as early-DCR), 22% (8/36) and 92% (33/36) at 4 months and 32% (9/28) and 82% (23/28) at 12 months (table 4). Of the 50 patients included, 14 patients did not perform the second follow-up assessment, due to liver progressive disease (n=10) leading to new antitumoural treatment (1 patient for extrahepatic disease), death (2 patients; 1 unrelated

Table 3

SIRT-related toxic effects				
	Grade 1-2 n (%)	Grade 3-4 n (%)	Grade 5 n (%)	Any grade n (%)
Hematological				
Lymphocytopenia	13 (26)	6 (12)	0	19 (38)
Thrombocytopenia	4 (8)	0	0	4 (8)
Hepatic				
Cytolysis	16 (32)	0	0	16 (32)
Anicteric cholestasis	12 (24)	3 (6)	0	15 (30)
Radio-induced liver disease	0	0	1 (2)	1 (2)
Abdominal				
Pain	12 (24)	0	0	12 (24)
Nausea	6 (12)	0	0	6 (12)
Vomiting	4 (8)	0	0	4 (8)
Diarrhea	2 (4)	0	0	2 (4)
Other				
Fatigue	11 (22)	0	0	11 (22)
Fever	1 (2)	0	0	1 (2)
Back pain	1 (2)	0	0	1 (2)
Groin pain	7 (14)	0	0	7 (14)
Groin hematoma	1 (2)	0	0	1 (2)
Inferior limbs ischemia	1 (2)	0	0	1 (2)
Right renal sub-capsular hematoma	1 (2)	0	0	1 (2)
Right hepatic artery dissection	1 (2)	0	0	1 (2)
Vasovagal syncope	1 (2)	0	0	1 (2)
Aspiration pneumonitis	1 (2)	0	0	1 (2)
Anorexia	1 (2)	0	0	1 (2)

Results are expressed as the worst toxic effect per patient, using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 5.0.

Table 4

Tumour response assessment according to RECIST 1.1			
	Early follow-up 1	Early follow-up 2	Late follow-up
Mean interval ± SD (months)	2.04 ± 0.69	4.08 ± 0.66	11.87 ± 1.68
Number of patients	50	36	28
Tumour response assessment			
CR, n (%)	0 (0)	0 (0)	1 (3.6)
Partial response, n (%)	8 (16)	8 (22.2)	8 (28.6)
Stable disease, n (%)	32 (64)	25 (69.4)	14 (50.0)
Progressive disease, n (%)	10 (20)	3 (8.3)	5 (17.9)
ORR, n (%)	8 (16)	8 (22.2)	9 (32.1)
DCR, n (%)	40 (80)	33 (91.7)	23 (82.1)

SD = standard deviation, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, ORR = objective response rate (CR + PR), DCR = disease control rate (CR + PR + SD.

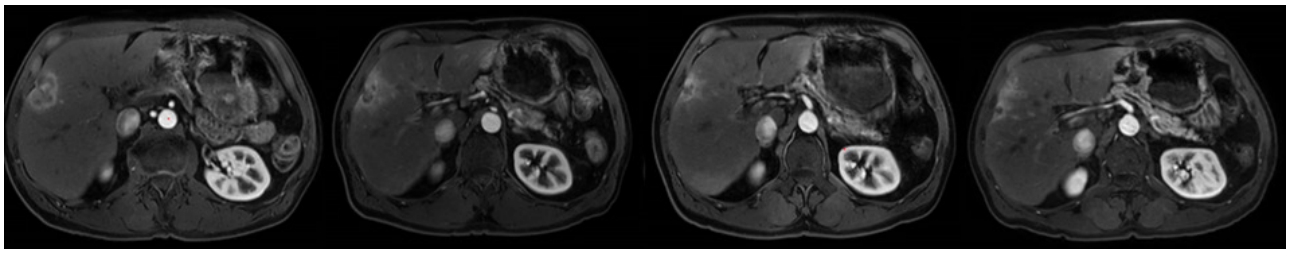

Figure 1. — MRI images from a patient who experienced partial response after radioembolization (from left to right: before treatment, at 2 months follow-up, at 4 months follow-up and at 12 months follow-up).

to disease) and SIRT liver toxicity (n=1). Twenty-two patients did not perform the late follow-up assessment due to liver progressive disease (13 patients), new anti-tumoral treatment (6 patients: 4 for extrahepatic disease progression, 1 for TACE due to persistent endocrine symptoms and 1 for therapeutic surgery) and death (3 patients: 1 related to tumour and 2 not related). Two patients showed progressive disease between 4 month follow-up and 12 months follow-up and were assessed at the 12 months follow-up time point.

As an example of a response to SIRT, we show MRI images from a responder patient in Fig. 1.

Chromogranin A (CgA) values were available for 19 patients. Correlation between CgA response and radiological response was not significant (Spearman r = 0.114, p=0.65), likewise the comparison between values

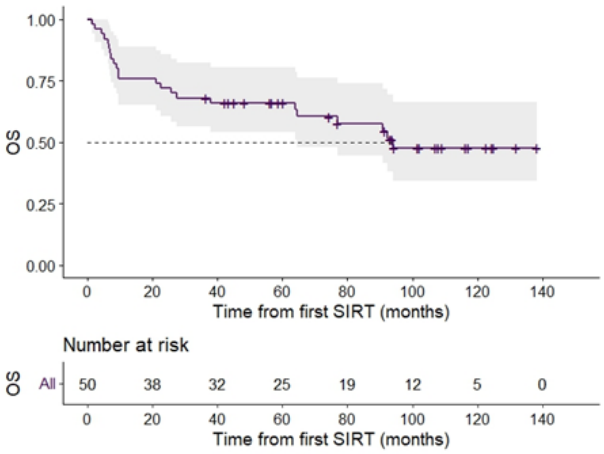

Figure 2. — Kaplan-Meier curve for overall survival (OS) in patients of the whole cohort.

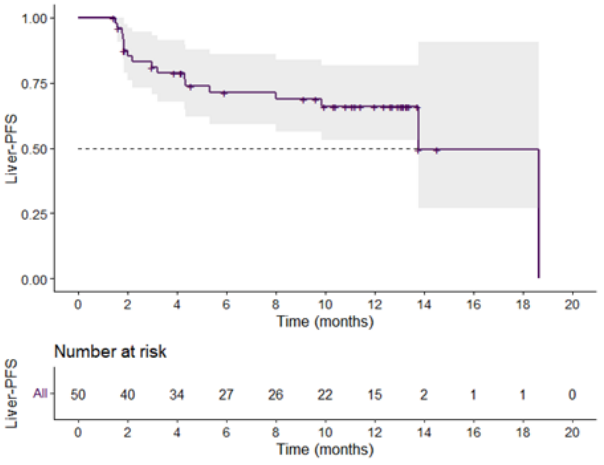

Figure 3. — Kaplan-Meier curve for liver-progression free survival (Liver-PFS) in patients of the whole cohort

after vs before SIRT (p=0.61). The number of neuron-specific enolase and 5-hydroxyindolacetic acid values was too low for analysis.

Clinical response

Ten patients presented NEN related symptoms: 5 patients had flushing, 3 patients diarrhea, 1 patient concomitant flushing and diarrhea and 1 patient hypoglycemia. Improvement of NEN related symptoms occurred in 7 of the 10 symptomatic patients (improvement in 4 out of 5 patients with flushing, 3 out of 3 with diarrhea, no improvement in patient with hypoglycemia and flushing + diarrhea).

Overall Survival and liver-progression free survival

Survival rates at 1, 2 years were 76% and 72% respectively (Fig. 2). Liver-PFS is illustrated in Fig. 3.

Significant prognostic factors were the same for OS and liver-PFS: NEN histological grade (3 versus 1+2) (hazard ratio (HR) for OS: 4.33 [1.77-10.57], for liver-PFS: 3.91 [1.34-11.37]) and early-DCR (HR for OS: 0.14 [0.05-0.37], for liver-PFS: 0.016 [0.003-0.078]). Kaplan-Meier curves regarding these prognostic factors are illustrated in Fig. 4. In the multivariate analysis, NEN histological grade and early-DCR remained significant for OS (HR 3.13 [1.20-8.16] and 0.20 [0.07-0.54] respectively) but only early-DCR remained significant for liver-PFS (HR 0.01 [0.00-0.11]) (Fig. 5).

There were no statistical differences in efficacy between SIR-Spheres and TheraSpheres .

Discussion

According to these data, SIRT achieved a very high disease control rate, the primary endpoint. This high DCR remained stable during one year of follow-up. Moreover, 72% of patients were alive 2 years after radioembolization. These results were particularly rele-vant given that 56% of patients had already received at least 2 prior treatments for metastatic disease and 44% of patients were suffering from grade 3 NEN. The proportion of G3 NEN patients was smaller in the previous larger trials : 10.2% (18) and 10% (12). As discussed previously, G3 NEN is a factor of poor prognosis. However, mOS was 20 months and mLiver-PFS was 10 months in this group (fig. 4A). Braat et al. (18) described a median survival of 10.8 months for patients with G3 tumors; authors do not provide detailed information on these G3 NENs. Our efficacy results are excellent and somewhat unexpected in such aggressive tumors. the median Ki67 was 26.3% (range 20-90%) and a majority of tumors were of pancreatic origin. Therefore, a priori, well differentiated tumors, this can in part explain the very good response rate in this subset population. Another explanation could be the very good uptake of spheres, based on a rigorous selection of our patients after the MAA arteriography. This is however a hypothesis, needing to be validated by detailed dosimetry.

SIRT had also showed clinical benefit, with a relief of NEN symptoms in 70% of cases (symptoms improved in 7 out of 10 symptomatic patients). Treatment was associated with a good safety profile, with only 18% of grade 3 AEs. Though, one patient died due to REILD.

There is currently no strong evidence supporting the efficacy of SIRT for the treatment for liver-only or liver-dominant metastatic NENs.

Indeed, the largest trial, published by Braat et al. (18), was a multicentric retrospective collection of 244 patients, that described a DCR of 91.3%. These results, together with those of Barbier et al. (12), were consistent with our findings.

PRRT was previously administrated to 4 patients who didn't develop any additional toxicity. Prognostic factors described in the literature were grade, early DCR, intrahepatic tumour load ≥ 75%, primary tumour, surgery of the primary, extrahepatic disease and elevated bilirubin (11,18,21,22). Among these, this study revealed that only low grade and early DCR were associated with

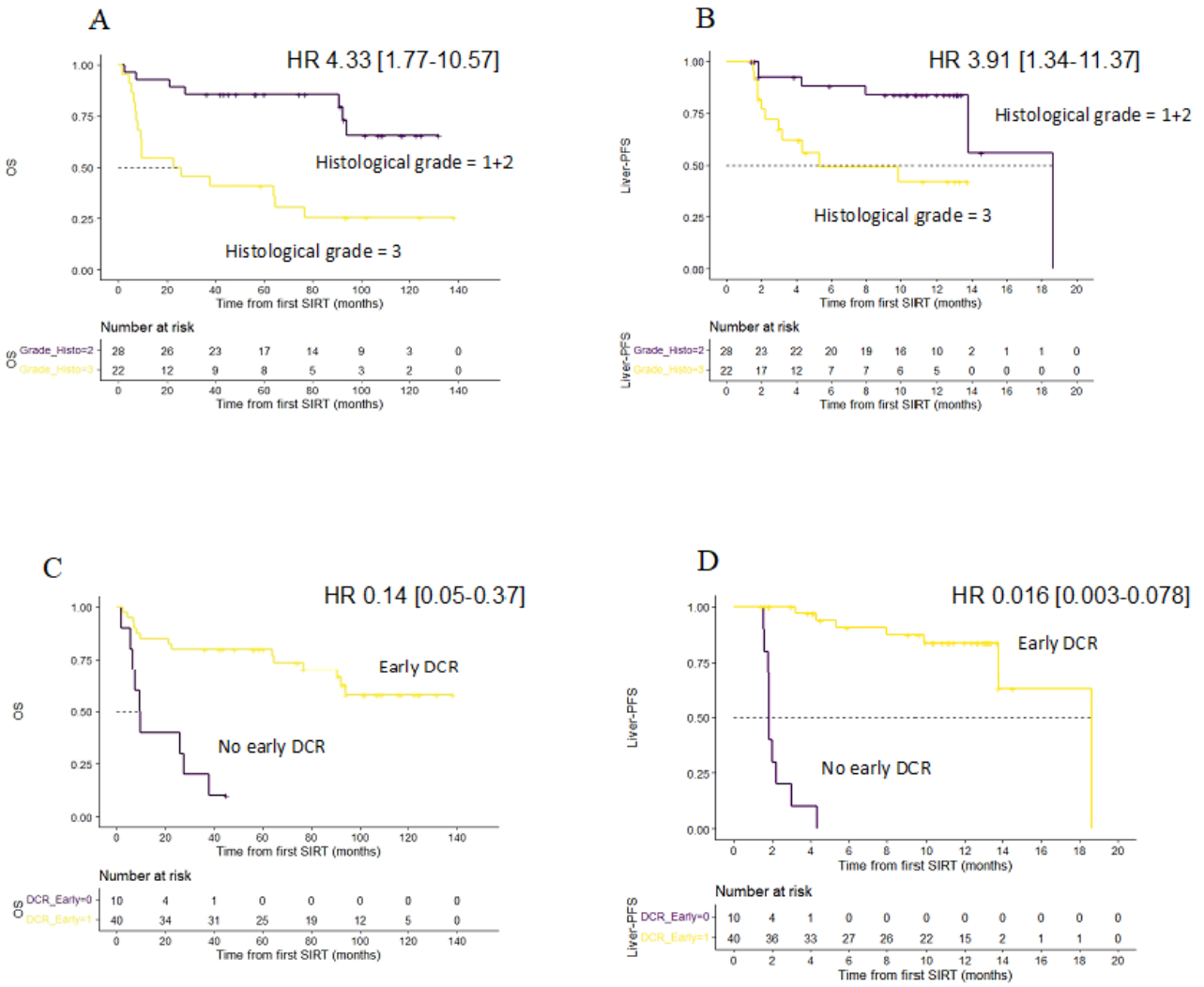

Figure 4. — Kaplan-Meier curves for overall survival (OS) and for liver-progression free survival (Liver-PFS) following histological grade (A + B) and disease control rate at 2 months (early-DCR) (C+D).

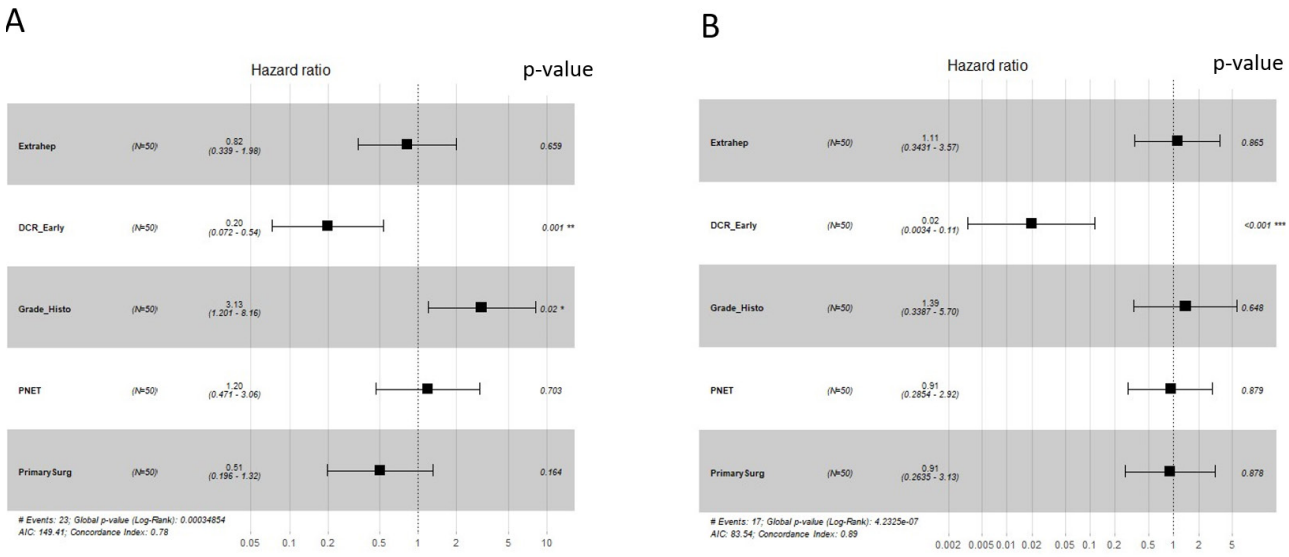

Figure 5. — Forest-plot of multivariate hazard ratios for overall survival (A) and liver-progression free survival (B) by prognostic factors Extrahep = Extrahepatic metastases, DCR_Early = early disease control rate, Grade_Histo = Histological grade, PNET = pancreatic neuroendocrine tumour, PrimarySurg = primary tumour site surgery.

a better OS and liver-PFS. Indeed, as selecting patient for SIRT adhered to published guidelines for eligibility criteria (3), patients with intrahepatic tumour load ≥ 75% and elevated bilirubin blood level were excluded. Interestingly, early DCR was a strong predictor of a better OS in the multivariate analysis. As showed in fig. 4D, OS was very poor when DCR was not achieved 2 months after SIRT, so clinicians should promptly propose a new course of treatment, as no benefit can be expected from SIRT for this minority of patients.

Severe toxicity was observed in 2 patients. One patient unfortunately died from REILD. The pre-SIRT SPECT-CT showed low uptake of MAA in some of the NELM compared to the normal liver tissue, after injection in the common hepatic artery. Consequently, the treatment was realized by selective left and right hepatic artery. Nevertheless, the Y90-Time-of-flight PET-CT performed at day+1 post-treatment showed low uptake in liver lesions. MRI performed 2 months later showed progressive disease. Acute liver failure was diagnosed 2 months after SIRT. This patient had a suspected underlying liver disease, possibly related to chronic alcohol consumption and had other co-morbidities (diabetes mellitus, hypertension, stage IIIB chronic renal failure). He was not treated by PRRT before. The second patient developed cirrhosis 5 years after the first SIRT - in total 2 SIRT were performed 2 years apart - no other risk factor was identified and SIRT was thus suspected as the primary cause of liver damage.

This study had limitations due to its retrospective design. First, some data related to histopathology were missing because biopsies were performed in another center for some patients. Secondly, CTCAE grading for clinical toxicities was performed with data available in the files. However, most of the studies assessing the value of SIRT to treat NELM were retrospective because of the heterogeneity and rarity of NEN. Some studies (12,18) have described better response rate following modified-RECIST (m-RECIST) but for logistical reasons, it was not possible to perform this analysis. As liver metastases are irrigated by hepatic artery, the assessment of viable tumors (tumoral tissue showing uptake in arterial phase of contrast enhanced imaging), m-RECIST offers undeniable added value. However, most prospective randomized studies evaluate OS and PFS with RECIST and not mRECIST. Prospective multicenter randomized controlled trials evaluating the role of SIRT in NELM would validate its use, but they are difficult to design, because of the rarity of the disease and the difficulty to choose a comparator treatment.

Conclusion

This study reported a single center cohort of NELM patients treated with SIRT, the patients were strictly selected according to guidelines, followed-up with a strict protocol and there was no lost to follow-up.

SIRT showed high efficacy in these patients, with a very good DCR, an acceptable safety profile and good NEN symptoms control. Although low NEN histological grade and mostly early DCR were associated with a better OS and liver-PFS, we believe that selected patients with G3 NENs can also benefit from SIRT, given the efficacy we observed in the large subset of G3 patients in our cohort. New line of treatment has to be rapidly proposed if there is no early DCR after SIRT. These data based on a single center experience with a strict protocol of follow-up and imaging added evidence to the value of SIRT for patients with NELM.

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