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Comparison of Transarterial Liver-Directed Therapies for Low-Grade Metastatic Neuroendocrine Tumors in a Single Institution

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Abstract

Objectives—We compared the clinical outcomes of patients with metastatic neuroendocrine tumors (mNET) treated with hepatic artery embolization (HAE), chemoembolization (HACE) and selective internal radiation therapy (SIRT) at our institution over the last ten years.

Methods—Medical records of 42 mNET patients with hepatic metastases treated with HAE, HACE or SIRT at the University of Iowa from 2001 to 2011 were analyzed.

Results—13 patients had HAE, 17 had HACE and 12 had SIRT as their initial procedure. TTP was similar between SIRT (15.1 months) and HACE/HAE groups (19.6 months) ($p=0.968$). There was a trend towards increased TTP in patients receiving HACE (33.4 months), compared to HAE (12.1 months) or SIRT (15.1 months), although not statistically significant ($p=0.512$). The overall survival for all patients from the first intervention was 41.9 months. There was no difference between HACE/HAE and SIRT in post-therapy change of CgA ($p=0.233$) and PcSt ($p=0.158$) levels. TTP did not correlate with the change in the post-therapy CgA ($p=0.299$) or PcSt ($p=0.208$) levels.

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The authors have no conflicts of interest or funding to disclose.

Conclusion—There was no significant difference in TTP in patients treated with SIRT compared to patients treated with HAE or HACE. Baseline and post-therapy marker changes were not predictive of TTP.

Keywords

neuroendocrine tumors; transarterial liver-directed therapies; chemoembolization; hepatic artery embolization; pancreastatin; chromogranin A

Introduction

Small bowel neuroendocrine tumors (carcinoid tumors) and pancreatic neuroendocrine tumors (pNETs) are relatively indolent malignancies that have a predilection for metastasizing to the liver¹. As many as 75% of small bowel and 30–85% of pancreatic neuroendocrine tumors present with synchronous or metachronous liver metastases². Liver metastases can result in significant morbidity from both overproduction of biologically active substances and mass effects. The presence of liver metastases is also associated with a poor prognosis, with an estimated 5-year survival rate of 22%³.

Surgical resection of metastases is the preferred method of treatment in patients with localized hepatic metastases; however, it rarely is an option in patients with multifocal disease⁴. Response rates for metastatic neuroendocrine tumors treated with systemic chemotherapy range from 0–38% with median overall survival ranging from 5 to 26 months⁵. Pancreatic NETs are more likely to respond to chemotherapy than small bowel NETs and can often be controlled temporarily with either systemic therapy such as everolimus, sunitinib or cytotoxic chemotherapy^{6–8}. Interferon has shown objective response rates in 4–7% of patients when studied in randomized clinical trials⁹. Somatostatin analogues are effective in controlling symptoms related to the disease and were recently shown to prolong progression-free survival in patients with metastatic small bowel NETs¹⁰. In vitro studies using Sandostatin have demonstrated an anti-proliferative effect on neuroendocrine cells; however, objective tumor responses are rarely seen in clinical practice⁴.

Liver directed therapies have been studied as a means of controlling disease progression in patients with hepatic metastases who are not candidates for liver resection. The typical indications for locoregional therapy in patients with liver metastases include control of symptoms related to overproduction of biochemically active substances or tumor bulk and rapid progression of liver disease⁵. Transcatheter arterial embolization has been studied as a means of treating liver metastases from neuroendocrine tumors. Liver metastases from NETs are typically hypervascular deriving the majority of their blood supply (80–90%) from the hepatic artery, while normal liver tissue derives its blood supply from the portal vein in addition to the hepatic artery. Normal liver parenchyma is preserved while ischemia is induced in the tumor tissue with transarterial liver-directed therapies. Transcatheter arterial embolization therapies have shown encouraging responses in survival outcomes and symptom palliation from both tumor bulk and hormone reduction. Prior research has shown that hepatic artery embolization (HAE) can reduce tumor size and palliate symptoms due to

carcinoid syndrome⁹. Hepatic artery chemoembolization (HACE) combines intra-arterial delivery of chemotherapeutics with particulate embolization and has several theoretical advantages over HAE: regional delivery of chemotherapy offers pharmacokinetic advantages compared with systemic chemotherapy, local cytotoxic effects of chemotherapy are combined with selective ischemia induced by embolization, and reduced blood flow by embolization can increase intratumoral drug concentration⁵.

Several studies have documented beneficial effects of both HAE and HACE in patients with metastatic neuroendocrine tumors. Retrospective studies have shown that HAE and HACE can reduce levels of biologically active substances, palliate symptoms and reduce tumor burden in many patients⁵. No randomized prospective trials comparing the different modalities have been performed. When compared in a retrospective fashion, the literature fails to demonstrate a difference in the response rates among these two procedures. Gupta et al. showed no statistically significant benefit of HACE in overall survival or radiographic response rate compared to patients treated with HAE alone⁹.

Selective internal radiation therapy (SIRT) is an emerging therapy for the treatment of liver metastases in neuroendocrine tumors that is being used increasingly more due to encouraging response rates, safety profiles and survival outcomes¹¹. Yttrium-90 is a beta-emitter that when delivered as radioactive microspheres (SIRT) can theoretically result in a more selective point source of radiation with higher tumor kill specificity when delivered into the tumoral and peritumoral vasculature⁵. In a retrospective multicentric study of 148 patients with liver metastases from neuroendocrine tumors treated with yttrium-90 microspheres (SIRT), stable imaging was noted in 22.7% of patients, partial response in 60.5%, and complete response in 2.7% of patients. No radiation liver failure occurred and the median overall survival was 70 months. The authors concluded that SIRT can safely deliver high doses of radiation to liver metastases from neuroendocrine tumors while producing a safety profile and treatment effect that is similar to other local liver-directed techniques³.

There are neither prospective nor retrospective studies comparing the efficacy and safety in patients treated with all three liver-directed therapies (HAE, HACE and SIRT) over a common time period. The goal of our study was to retrospectively analyze the clinical, biochemical and radiographic response rates of patients treated with these treatment modalities at our institution over a 10-year period.

Materials and Methods

After an approval was obtained from the Institutional Review Board of the University of Iowa, we identified and retrospectively analyzed the medical records of 42 patients with neuroendocrine tumors liver metastases treated at the University of Iowa Hospitals and Clinics (UIHC) with hepatic artery bland embolization (HAE), chemoembolization (HACE) or selective internal radiation therapy (SIRT) from 2001 until 2011. Information was obtained from the electronic medical records, including patients' demographic data, pathology reports, radiology images, and outcome data. In all patients the pathology specimens were reviewed at the UIHC by staff pathologists to confirm the diagnosis. The

location of the primary tumor was recorded, as was the presence or absence of extra-hepatic metastases based on imaging studies (CT, MRI, bone scan, ultrasound, or Octreoscan).

The choice of liver-directed therapy was determined at the discretion of the referring physician and the interventional radiologist. All patients had adequate liver and renal functions prior to the procedure (bilirubin < 2 mg/dL, serum creatinine < 2 mg/dL). The decision to proceed with therapy was typically based on progression of symptoms non-responsive to octreotide therapy or rapid progression of liver tumor burden on imaging. Patients who had received prior systemic chemotherapy and/or peptide receptor radionuclide therapy (PRRT) were allowed in this study. Patients typically had a pre-therapy CT of the abdomen and pelvis or abdominal ultrasound within one month of initiation of the liver-directed therapy. Diagnostic angiography was performed by an interventional radiologist before the treatment procedure and consisted of celiac and superior mesenteric angiography to evaluate the hepatic arterial anatomy. The entire liver lobe was treated whenever possible if one lobe was involved. If both lobes were involved, a staged procedure was performed with embolization of the second lobe occurring four to six weeks later. Response criteria were evaluated chronologically after the first procedure with the liver lobe with the greatest degree of disease treated first. After the hepatic artery was catheterized, embolization consisted of 300–500 micron size polyvinyl alcohol (PVA) microspheres or Gelfoam powder. Embolization was continued until there was complete or near-complete stasis of flow. A post-embolization angiogram was performed to determine resolution of tumor blush. Chemoembolization consisted of intra-arterial doxorubicin, streptozocin or cisplatin followed by Gelfoam slurry or PVA microspheres. Selective internal radiation therapy (SIRT) was performed with yttrium-90 SIR-Spheres®. Patients were hospitalized for at least one night after the procedure and discharged the following day depending on symptomatology and laboratory results. All patients received subcutaneous octreotide administered prior to the procedure.

Follow-up imaging was typically obtained within 1–2 months after the first intervention and then at least every 3–6 months for the first 2–3 years. Radiographic assessment after therapy was based on the radiologist's interpretation. A response was defined as any radiographic reduction in the size of liver lesions, progression – as development of any new lesions without regression of pre-existing lesions, or if there was growth of pre-existing lesions, and mixed response - as reduction in size of some pre-existing lesions with accompanying growth of others and/or development of new lesions. Follow-up CT or MRI images were compared to prior images by staff radiologists at UIHC. Evaluation of radiographic progression was based on the date of the first follow-up image demonstrating an increase in size or number of liver lesions.

Symptomatic response to therapy was assessed within the first 3 months post-therapy among patients who were documented to have prior symptoms from their neuroendocrine tumor (i.e. fatigue, abdominal pain, flushing, diarrhea, nausea, palpitations, etc.). Symptomatic patients were evaluated for either a significant improvement in symptoms, absence of significant improvement in the symptoms, or worsening of the symptoms. Subjective symptoms were evaluated by using data obtained from the clinic charts containing patient and physician assessments. Adverse events with nausea, vomiting, abdominal pain or fever

were also recorded for each procedure based on the inpatient discharge summary post-procedure and on the first clinic follow-up note.

Tumor markers levels for chromogranin A (CgA) and pancreastatin (PcSt) were assessed to determine response to therapy. Markers levels were recorded pre-procedure, post-procedure within 1–6 months, then yearly post-procedure up to 5 years when available. Given the varying reference ranges for the markers levels over time, the values were standardized by dividing the marker value by the maximum reference range value for each laboratory and then configured as a mean value. ANOVA was used to compare the pre-therapy mean marker level value among the liver-directed therapies to assess for a difference. The difference of the 6-month mean post-therapy marker level was compared to the pre-therapy mean marker and then compared among the various liver-directed treatment groups to assess for differences in marker change. Cox proportional hazards regression method was used in univariate analyses to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the post-therapy tumor markers from the pre-therapy markers to determine if they are predictive of overall survival or time-to-progression.

Time-to-progression (TTP) and overall survival (OS) curves were constructed using the Kaplan-Meier method with comparisons using Wilcoxon Rank Tests. Overall survival was determined from the first liver-directed therapy to the date of death or to the date of last follow-up for patients who were still alive at the time of last follow-up. Radiographic TTP was calculated from the first liver-directed therapy until the date of radiographic progression, death or last follow-up for those patients who did not progress. Categorical data was compared using Pearson Chi-Square Tests. Univariate Cox proportional hazards regression models were used to evaluate the predictive effect of each factor alone. All statistical analyses were completed using JMP software®. Statistical significance was defined as $P < 0.05$.

Results

Patients

Between 2001 and 2011, 42 patients with hepatic neuroendocrine metastases underwent treatment with HAE, HACE or SIRT at the University of Iowa Hospitals and Clinics. The median age of the patients was 56.5 years (range 36–81 years). There was equal distribution among the sexes with 21 women and 21 men. Ten patients had extra-hepatic metastases and all patients were on somatostatin analogues at the time of the intervention. The primary tumor was located in the small bowel in 48 % of patients (Table 1). Eight patients had pancreatic primary tumors (19%), and eight patients had no known primary tumors (19%).

Treatment

Thirteen patients were treated initially with HAE (31%), seventeen with HACE (40%), and twelve with SIRT (29%). Twenty of the forty-two patients had a second procedure. Nine patients had HAE as their second procedure (45%), five had HACE (25%) and six had SIRT (30%).

Symptomatic Response

Prior to their first liver-directed therapy, twenty-seven patients were symptomatic from their liver metastases. Among symptomatic patients, there was no statistically significant difference in symptomatic improvement between HACE (6/13), HAE (4/8) and SIRT (5/6) ($p=0.265$) at 3 months after their first liver-directed therapy (although most patients undergoing SIRT experienced relief of symptoms) (Figure 1). Following the second procedure, six patients who were symptomatic reported improvements in their symptoms: HACE 1/3, SIRT 2/4, HAE 3/5.

Adverse Events

There were no deaths due to liver-directed therapy in this cohort. The majority of patients were hospitalized overnight following the procedure. The most common adverse events were nausea, vomiting, abdominal pain and fever. Twenty-one patients (50%) had nausea following their first liver-directed therapy. There was no significant difference between HAE/HACE and SIRT in post therapy vomiting ($p=0.470$), fever ($p=0.236$) or abdominal pain ($p=0.139$). One patient receiving HACE had a grade 3 elevation in liver enzymes after the first procedure and two patients had a grade 1 elevation in liver enzymes following the second procedure (HACE and HAE).

Radiographic Response

There was no difference in initial radiographic response between the three treatments at 6 months following the first procedure ($p=0.134$) (Figure 2). Responses were seen in 7/17 patients treated initially with HACE (41%), 4/12 patients treated with HAE (33%), and 6/12 patients treated with SIRT (50%). Three patients receiving HACE and one patient receiving SIRT had progressed at 6 months after the first intervention. Mixed response following the first intervention was seen in three patients receiving SIRT, one patient receiving HAE and four patients receiving HACE.

Progression and Survival

The median time-to-progression was 19.2 months after the first intervention (Figure 3) with a 5-year PFS of 15%. There was no significant difference in TTP after the first intervention between SIRT (15.1 months) and HAE or HACE (19.6 months) ($p=0.968$) (Figure 4). Although not statistically significant, there was a trend towards an increased time-to-progression in HACE (33.4 months), compared to HAE (12.1 months) or SIRT (15.1 months) ($p=0.512$) when the three treatment groups were compared (Figure 5). On univariate analysis, the four primary tumor sites in this cohort – small bowel, pancreas, lung and unknown primary- were well-distributed among the three treatment groups, suggesting tumor site did not influence response to therapy ($p=0.57$). Also on univariate analysis, there was no difference in TTP among patients with these four tumor sites ($p=0.37$).

The median overall survival for the entire group from the first liver-directed therapy was 41.9 months (Figure 6) and the 5-year overall survival from the first intervention for the entire group was 45%. There was no significant difference in median overall survival among patients in the three different treatment groups ($p=0.300$) although patients undergoing

HACE numerically had the longest survival. The median overall survival for HAE was 21.3 months, HACE 68.7 months and SIRT 26.8 months.

Tumor Markers

There was no difference in pre-procedure mean chromogranin A (CgA) among patients receiving their first treatment of SIRT (56.43) or HA(C)E (22.87) ($p=0.1913$) or pre-procedure mean pancreastatin (PcSt), SIRT (17.67) or HA(C)E (17.95) ($p=0.9824$). At six months post-first procedure, there was no difference between SIRT or HA(C)E in the change in CgA ($p=0.234$) or PcSt ($p=0.158$). There was no correlation between TTP and pre-therapy CgA ($p=0.131$) or PcSt ($p=0.654$) in any of the treatment groups (Table 3). Overall survival also did not correlate with the pre-therapy CgA ($p=0.606$) or PcSt ($p=0.597$). The change in PcSt at 6 months post-therapy was not predictive of TTP ($p=0.2071$) or OS ($p=0.313$). Although the change in CgA at 6 months post-therapy was not predictive of TTP ($p=0.299$), a decrease in CgA was associated with an increase in OS ($p=0.037$).

Discussion

Liver metastases are an influential predictor of survival in patients with metastatic neuroendocrine tumors irrespective of the primary tumor site³. A 13–54% estimated 5-year survival of patients with untreated neuroendocrine liver metastases relative to 75–99% 5-year survival for those patients without liver metastases indicates the prognostic power of liver metastases³. Surgical interventions for neuroendocrine liver metastases have been shown to have improved outcomes compared to nonsurgical approaches; however, surgery is an option for only a small percentage of patients with liver involvement¹². Recently there has been a significant evolution in the management of patients with non-resectable liver metastases.

Liver-directed therapies have been studied as a means of improving survival, reducing tumor burden and minimizing symptoms caused by excessive hormone secretion in patients with liver metastases from neuroendocrine tumors¹¹. Hepatic transarterial embolization (HAE) and chemoembolization (HACE) have historically been the most widely utilized embolization strategies in this patient population. Both techniques have demonstrated improvements in symptomatic control, although there has been no consensus if the addition of chemotherapy to bland embolization is of clinical relevance¹³. The survival benefits of liver-directed therapy have not been confirmed in a clinical trial. Selective internal radiation therapy (SIRT) with Y-90 microspheres is another liver-directed therapy that has evolved as a method of mechanically targeting liver metastases with very high irradiation doses¹⁴. Retrospective studies evaluating the efficacy of SIRT in patients with neuroendocrine liver metastases have concluded that SIRT has a treatment effect and safety profile that is comparable to other local techniques³. No studies, however, have directly compared SIRT to HAE or HACE.

To our knowledge, our study is the first retrospective comparison of all three liver directed therapies in a population of patients with metastatic neuroendocrine tumors treated within

one medical center. None of the patients in this study were candidates for resection and all patients were on somatostatin analogues at the time of liver-directed therapy.

There was no difference in overall radiographic response among the three treatment groups at 6 months post-first procedure. The average radiographic response rates ranging from 33% to 50% are similar to data demonstrated in other studies. King et al. reported a complete and partial response rate of 18% and 32% respectively in a 34-patient cohort retrospective study of patients treated with SIRT combined with 5-FU, which is similar to the overall response rate of 50% among patients treated with SIRT in this study^{3,15}.

Our study did not use RECIST criteria in calculation of radiographic response, but instead relied on radiology reports. At our institution almost all CT studies are read by dedicated body CT radiologists, so we did not feel it was unreasonable to extract response data from radiology reports. This approach allowed simple classification: no response, response, mixed, or progression. Furthermore, this approach is reflective of clinical practice. We recognize the inherent bias associated with the radiologist's overall subjective approach to analyzing response as well as the limitations related to not using established response criteria.

Sixty-four percent of patients were symptomatic from liver metastases at the time of their first-liver directed therapy. Fifteen patients gained improvement in their symptoms (56%), although we found no difference in symptomatic improvement among the three therapies at 3-months post-treatment. Paprottka et al. noted a 94.7% improvement in symptoms at 3-month post-procedure in 42 patients treated with SIRT¹³. In a retrospective analysis of 122 patients treated with HACE, Bloomston et al. noted a symptomatic improvement in 92% of patients with a significant amount of patients either decreasing or discontinuing usage of octreotide¹. The small sample size and retrospective nature of symptom data collection used to assess this clinical endpoint was prohibitive in quantitatively assessing response to each specific symptom caused by a neuroendocrine tumor. We recognize this significant limitation in symptom assessment in this current study.

Tumor markers such as chromogranin A and pancreastatin are frequently utilized to predict outcome and assess response to therapy. While elevated markers seem to predict worse survival, little data exists on changes in marker levels after liver-directed therapy. There was no difference in the post-therapy change in either the pancreastatin or chromogranin A between SIRT and HAE or HACE. Post-therapy marker changes did not predict radiographic TTP in this study. Pancreastatin has, however, been shown to have sensitivity in predicting response to therapy in other studies. Bloomston et al. reported that a 20% reduction in pancreastatin was predictive of improved survival in patients treated with HACE, and a pre-HACE pancreastatin level > 5,000 pg/ml was predictive of inferior survival¹.

Severe adverse events did not occur with significant frequency in this study and no death occurred. The most common adverse event was nausea, followed by fever, abdominal pain and vomiting. SIRT did not have increased toxicity compared to HAE or HACE and the toxicity profile overall was acceptable for all modalities. Paprottka et al. also demonstrated

SIRT is safe with no severe acute or delayed toxicities¹³. Other studies have shown that chemoembolization was not associated with a higher degree of toxicity compared to bland embolization¹⁴.

In this current study, SIRT did not prolong time to radiographic progression compared to patients treated with either HAE or HACE. Although patients treated with HACE seemed to have a longer median time-to-progression (33.4 months) compared to patients treated with HAE (12.1 months) or SIRT (15.1 months), this was not statistically significant. The lack of statistical significance among these treatment groups despite substantial differences raises concerns for a type II error that could potentially have been overcome with a larger cohort size. During the study period, chemoembolization and bland embolization were utilized more often earlier in the study cohort at our institution compared to SIRT, which was increasingly utilized later in the study. As such, the longest observation period was seen in patients undergoing HACE, which may account for the favorable TTP. In a 42-patient prospective comparison of SIRT to HACE with DEBOX beads in patients, Whitney et al. reported a median PFS of 14 months in patients treated with SIRT which is comparable to our observation¹⁶.

The time to radiographic progression among liver-directed therapies in this study is comparable to other published studies. In a prospective single-center study of 9 patients treated with SIRT, Kalinowski et al. reported a TTP of 11 months^{2,17}. Gupta et al. analyzed PFS between patients treated with HAE or HACE and found no differences in small intestinal tumors (20.9 vs 23.9 months respectively) or pancreatic islet cell tumors (14.1 vs 18.9 months respectively)⁹. Maire et al. found no difference in TTP among 12 patients treated with HAE reporting a median TTP of 24 months and 14 patients treated with HACE reporting a TTP of 19 months^{14,18}. Based on these studies, HACE has not been proven to be superior to HAE in increasing time to radiographic progression.

Patients in this study also experienced a prolonged survival after any of the three liver-directed therapies. Because of the small number of patients and exposure to other modalities of treatment, we found it difficult to definitively compare differences in overall survival among these treatment groups. There was no difference in overall survival among the three treatment groups noted. The median overall survival of patients treated with SIRT in this study was 26.8 months. Rhee et al. noted a median overall survival of 22 to 28 months in 42 patients treated with SIRT,^{11,19} while King et al. combined SIRT with infusional 5-FU in 34 patients with unresectable neuroendocrine liver metastases and observed a median OS of 27.6 months¹⁵. Kennedy et al. performed a retrospective review of 148 patients treated with SIRT at 10 clinical centers and noted a median overall survival of 70 months²⁰. The timing at which SIRT was used in the clinical course might explain the relative lower median OS of patients treated in the current study.

The median overall survival of patients treated with HAE and HACE in this study was 21.3 months and 68.7 months respectively. Gupta et al. compared HACE to HAE in 69 patients with carcinoid tumors and also found no difference in overall survival (33.8 vs 33.2 months respectively)⁹. In an 84-patient study of HAE, Strosberg et al. noted a 36-month median overall survival⁴. Bloomston et al. found a median overall survival of 33.3 months in 122

patients treated with HACE¹. The indolent nature of this tumor in addition to variation in the timing of liver-directed therapy might explain the differences in median overall survival found among these differing treatments.

Conclusion

Liver-directed therapies are beneficial in prolonging time to progression in patients with NETs metastatic to the liver who are not candidates for liver resection. The optimal liver-directed therapy for metastatic neuroendocrine tumors remains unknown. In this cohort, no single liver-directed therapy was superior to another in overall radiographic response, time to radiographic progression, symptom reduction or development of toxicity. The overall survival after all three liver-directed therapies is relatively long. Randomized clinical trials to better understand how these therapies compare to one another are needed.

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Figure 1.
Symptom response among patients who were symptomatic following their first liver-directed therapy.

Figure 2.
Radiographic response at 6-months following their first liver-directed therapy.

Figure 3.
Overall time-to-progression after first liver-directed therapy.

Figure 4.
Comparison of time-to-progression among SIRT and either HAE or HACE (HA(C)E) following the first liver-directed therapy.

Figure 5.
Comparison of time-to-progression among HAE, HACE and SIRT following the first liver-directed therapy.

Figure 6.
Overall survival following the first-liver directed therapy.

TABLE 1

Primary Tumor Location

Location	No.
Cecum	1
Colon	1
Duodenum	1
Ileum	19
Lung	2
Pancreas	8
Small bowel unspecified	1
Stomach	1
Unknown Primary	8

TABLE 2**Tumor Marker Descriptive Data**

	n	Mean	P
Pretherapy CgA[*]	29	36.76	
HACE/HAE	17	22.87	0.1913
SIRT	12	56.43	
HACE	4	5.02	
HAE	13	28.36	0.3603
SIRT	12	56.43	
Before 6 month CgA[†]	26	-32.289	
HACE/HAE	15	-74.16	0.2337
SIRT	11	24.80	
HACE	3	-33.38	
HAE	12	-84.35	0.4650
SIRT	11	24.80	
Pretherapy PcSt[*]	34	17.85	
HACE/HAE	22	17.95	0.9824
SIRT	12	17.67	
HACE	10	22.41	0.8711
HAE	12	14.24	
SIRT	12	17.67	
Before 6 month PcSt[†]	28	3.50	
HACE/HAE	17	0.35	0.1581
SIRT	11	8.36	
HACE	7	1.18	
HAE	10	-0.23	0.3695
SIRT	11	8.36	

Markers were standardized by dividing the marker value by the maximum reference range value for each laboratory and then configured as a mean value.

CgA = chromogranin A; PcSt = Pancreastatin.

^{*} Pretherapy CpA/PcSt represents the mean value before liver-directed therapy.

[†] Before the 6 month CgA/PcSt represents the difference of the mean between the pretherapy and 6 month posttherapy marker. Negative values represent a decrease in the mean tumor marker at 6 months posttherapy compared with a pretherapy marker.

TABLE 3

Tumor Marker Univariate Analysis of OS and Progression-Free Survival

	OS			TTP				
	HR	95% CI	p	HR	95% CI	p		
Pretherapy CgA	1.004	0.988	1.021	0.6058	0.981	0.956	1.006	0.1311
Before 6 month CgA	0.993	0.987	1.000	0.0367	0.999	0.997	1.001	0.2987
Pretherapy PcSt	1.006	0.984	1.028	0.5969	0.996	0.978	1.014	0.6535
Before 6 month PcSt	0.971	0.916	1.028	0.3128	0.975	0.936	1.014	0.2077