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LIVER CANCER

Long acting octreotide in the treatment of advanced hepatocellular cancer and overexpression of somatostatin receptors: Randomized placebo-controlled trial

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Abstract

AIM: To estimate if and to what extent long acting octreotide (LAR) improves survival and quality of life in patients with advanced hepatocellular carcinoma (HCC).

METHODS: A total of 127 cirrhotics, stages A-B, due to chronic viral infections and with advanced HCC, were enrolled in the study. Scintigraphy with ^{111}Indium labeled octreotide was performed in all cases. The patients with increased accumulation of radionuclear compound were randomized to receive either oral placebo only or octreotide/octreotide LAR only as follows: octreotide 0.5mg s.c. every 8 h for 6 wk, at the end of wk 4-8 octreotide LAR 20 mg i.m. and at the end of wk 12 and every 4 wk octreotide LAR 30mg i.m.. Follow-up was worked out monthly as well as the estimation of quality of life (QLQ-C30 questionnaire). Patients with negative somatostatin receptors (SSTR) detection were followed up in the same manner.

RESULTS: Scintigraphy demonstrated SSTR in 61 patients. Thirty were randomized to receive only placebo and 31 only octreotide. A significantly higher survival time was observed for the octreotide group (49 ± 6 wk) as compared to the control group (28 ± 1 wk) and to the SSTR negative group (28 ± 2 wk), LR = 20.39, df = 2, $P < 0.01$. The octreotide group presented 68.5% lower hazard ratio [95% CI (47.4%-81.2%)]. During the first year, a 22%, 39% and 43% decrease in the QLQ-C30 score was observed in each group respectively.

CONCLUSION: The proposed therapeutic approach has shown to improve the survival and quality of life in SSTR positive patients with advanced HCC.

Key words: Hepatocellular cancer; Somatostatin; Long acting octreotide; Somatostatin receptors; Quality of life

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INTRODUCTION

Hepatocellular carcinoma (HCC) ranks eighth in frequency among malignancies worldwide, representing the third largest cause of cancer-related death, with an estimated mortality rate of about one million deaths annually and an incidence-to-mortality ratio very close to one[1,2]. In Mediterranean countries, HCC occurs mainly in patients with cirrhosis due to chronic infection by hepatitis B (HBV) and C (HCV) viruses and/or alcohol consumption. Cirrhotic males with increased alpha-fetoprotein (AFP) levels present the highest risk[3-5]. There is no data to propose a therapeutic algorithm for HCC to be implemented globaly. Liver transplantation (from cadaveric or living donors), surgical resection and percutaneous ethanol injection (PEI) and transcatheter arterial chemoembolizatin (TACE) achieve a relatively high response rate and can be classified as curative or effective treatment modalities, but only in selected candidates with small (< 5 cm) tumors[3-10]. Radio-frequency thermal ablation, microwaves, laser photocoagulation and cryosurgery are relatively new therapeutic methods with effectiveness sometimes comparable to PEI, but the experience is still limited[11-15]. Unfortunately, these therapies might only be effective in 30% of patients with HCC, whereas the remaining may benefit only from palliative

therapeutic approaches such as intraarterial administration of radionuclear compounds or chemotherapeutic agents, systemic chemotherapy, hormone or vitamine administration and several combinations of the methods reported above with controversial impact on survival and quality of life[15-20]. Somatostatin and its synthetic analogues, octreotide and lanreotide, play an important role in the management of gastroenteropancreatic neuroendocrine tumors through peptide suppression and antiproliferative plus apoptosis-inducing mechanisms[21-23]. Five cell-surface somatostatin receptors (SSTR), SSTR-1 through SSTR-5, have been characterized. Based on structural similarity and reactivity for the hexapeptide and octapeptide somatostatin analogues, SSTR-2, 3 and 5 belong to the same SSTR subclass. SSTR-1 and 4 react poorly with these analogues and belong to a separate subclass[24]. The presence of SSTR on the human HCC cells have not been adequately studied. A study of Reubi *et al*[25] reports that 41% of the HCC tissue samples overexpressed SSTR and 47% expressed vasoactive intestinal peptide (VIP) receptors with high affinity for somatostatin and octreotide. Further studies demonstrated high detection rates of SSTR 2,3 and 5 in HCC cells, although with high heterogenicity even in the same tumor, but also with high affinity to octreotide[26-28]. Somatostatin receptor scintigraphy (Octreoscan: Mallinckrodt Medical, Petten, Holland) currently is recognized as the gold standard for imaging of SSTR-2 and 5 positive tumors[29,30]. With an overall sensitivity ranging between 80% and 90%, it is effective in detecting primary and metastatic lesions not apparent by conventional imaging techniques in patients with neuroendocrine tumors, except insulinomas, and also in patients with small cell lung cancer, meningioma, breast cancer and astrocytomas[29,31]. Besides confirming the diagnosis and localizing tumor, somatostatin receptor scintigraphy has proved useful in predicting response to cold somatostatin analog treatment[32]. The administration of octreotide as monotherapy, in patients with advanced HCC, has achieved controversial results[33-36].The major drawback of the studies performed until now, was the unknown presence or not of SSTR in the tumor of patients of the treated and the control group.

The primary end point of the present placebo-controlled clinical trial was to estimate if and to what extent the administration of Octreotide Acetate Long-Acting Formulation (Sandostatin LAR) improves survival rate of patients with HCC-SSTR positive and A-B stage cirrhosis with respect to tumor size and AFP levels. The secondary end point of the study was to evaluate the quality of life of these patients.

MATERIALS AND METHODS

Design of the study

The present study is a randomized placebo-controlled clinical trial. Sixty-one patients with hepatocellular carcinoma and overexpression of SSTR in the tumor were allocated into the two treatment arms, of whom thirty received only oral placebo (control group) and 31 received only octreotide (octreotide group). Patients' allocation into the two treatment arms was based on a sequence of random binary numbers (i.e. 111100111010 …) that was developed in a computer based program. A value of 1 allocates patients in the group of octreotide and a value equal to 0 in the placebo group. Furthermore 66 patients, with negative scintigraphic findings, did not receive any treatment (SSTR-negative group). No differences regarding gender and age were observed among the study groups ($\chi^2 = 3.47$, df = 2, $P > 0.05$ and $F = 0.009$, df = 125, $P > 0.005$ respectively).

The duration of follow-up was scheduled to be 3 years. A total of 127 patients, 78 men and 49 woman, with advanced HCC (unresectable tumor, metastatic disease, not suitable for TACE) and cirrhosis stage A or B, after written informed consent, according to bioethical principles in medical research and the declaration of Helsinki (Revised 1983), were enrolled in the study. The study protocol was approved by the hospital ethics committee. Exclusion criteria was cirrhosis stage C, portal vein thrombosis, Karnofsky score > 70%, clinical hepatic encephalopathy, previous treatment for HCC and previous somatostatin/somatostatin analogues administration for other reasons. All patients had liver cytology (fine needle aspiration-FNA CT guided) compatible with the disease. We preferred FNA in place of guided liver biopsy because of the realiability of the method and the minor risk of complications[37]. The morphology of the tumor, according to the gross classification of Eggel, was as follows: massive type (> 6 cm) 87 patients, 53 men and 34 women, multinodular type (> 4 nodules or 3 nodules more than 4 cm one of them in diameter) 26 patients, 15 men and 11 women, and diffuse type 14 patients, 11 men and 3 women. The etiology was: chronic HBV infection 59 patients, 39 men and 20 women, chronic HCV infection 62 patients, 37 men and 25 women, and chronic HBV and HCV co-infection 6 patients, 3 men and 3 women. An additional history of alcohol abuse was noted in 16 patients, 9 (8 men, 1 woman) with chronic HBV infection, 6 (4 men, 2 women) with chronic HCV infection and 1 (man) with HBV and HCV co-infection.

Scintigraphy with ^{111}Indium-labeled octreotide was performed in all patients after confirmation of diagnosis, for determination of SSTR. For the uptake of the radiopharmaceutical ^{111}Indium-labeled octreotide in our study we applied the Krennings' score. According to this: score zero means no abnormality, one means faint uptake, two means clear uptake in the tumor, but less than in the liver, score three means a higher uptake than that in the liver and four shows that there is increased accumulation in the tumor[38].The images were visually analyzed by two blinded independent observers, specialists in nuclear medicine, with disagreements resolved by consensus. The variability rate between the observers was low, almost 10%.

The patients with increased uptake of radionuclear compound in the liver, Krenning's score three and four, were randomised to receive either only oral placebo or only octreotide s.c. and octreotide long-acting formulation i.m. (Sandostatin and Sandostatin LAR; Novartis, Basel, Switzerland) as follows: octreotide 0.5 mg s.c. every 8 h for 6 wk. At the end of wk 4 and 8 octreotide LAR 20 mg i.m. For the period between wk 4 and 6 octreotide

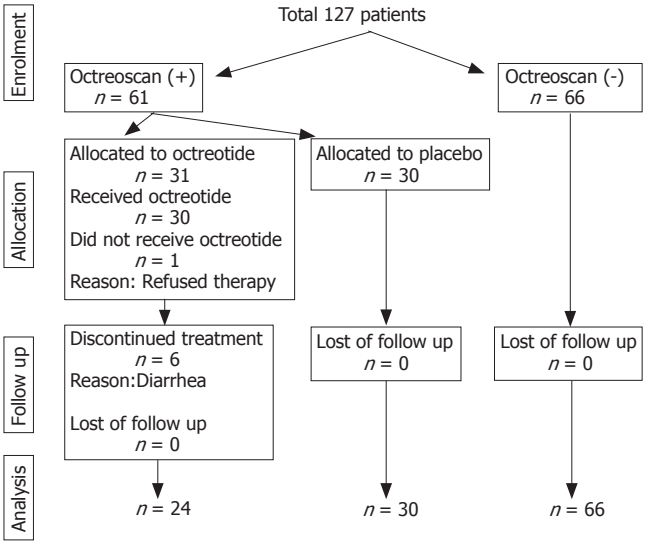

Figure 1 Flowchart of study patients.

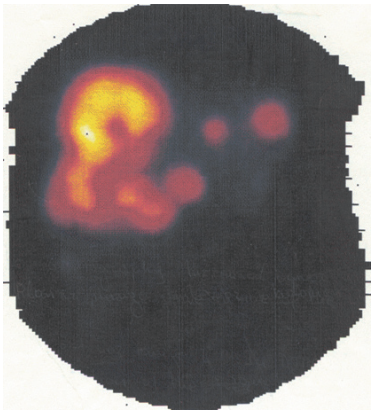

Figure 2 Increased uptake of ^{111}Indium labeled octreotide in the right hepatic lobe. Somatostatin receptor positive scan.

0.5 mg was given s.c. every 8 h simultaneously. At the end of wk 12 and every 4 wk octreotide LAR 30 mg. All intramuscular injections were performed by the staff of our unit. The therapeutic regimen reported above was performed because of the kinetics of octreotide release and time to achieve therapeutic concentrations of the drug from the LAR formulation. Octreotide or placebo were administered until patient withdrawal or death.

The baseline assessment included physical and laboratory examination (complete blood count, prothrombine time, AFP levels, liver biochemistry and renal function tests) as well as measurement of the tumor size using dual phase helical CT scans. All patients had a monthly follow up with the laboratory tests reported above and every 2 mo including AFP measurements.

The size of the tumor was reassessed with CT scans at 3-mo intervals. All hematological and biochemical tests were performed at the central hospital laboratory. The quality of life was determined monthly, performed by an experienced psychiatrist in oncology patients, and was based on the QLQ C30 questionnaire proposed by EORTC[39]. Patients with negative SSTR detection were followed up in the same manner.

Statistical analysis

This was a randomised clinical trial, designed to enroll 130 patients of either sex, and to follow them up for 3 years. Sample size calculation was based on the assumption of 65% evaluate at the end of follow-up on the basis of a sided 5% hypothesis and 80% statistical power. At least 55 events would be required to detect statistical difference.

Summary statistics are presented as mean ± SE. Time related variables are presented as median and 1st to 3rd quartiles, in order to avoid the effect of extreme values on arithmetic mean. Qualitative variables are presented as absolute and relative frequencies. Death rates were calculated using the observed person-time, in weeks. The proportion of surviving persons has been recorded every one-week. Univariate analysis (comparisons between groups of the study and time to event) was based on the calculation of the Log-rank test. Multivariate analysis was performed using the Cox proportional hazards model with all cause death as end point and age, sex, etiology, and morphology as potential covariates. The association between the treatment arms and the fatal events are presented as exponentials (hazard ratios) of the estimated coefficients using the SSTR-negative group as the reference category. The goodness-of-fit test was based on comparing the observed survival probability with the expected under the assumption of proportional hazards. The assumption of proportionality was graphically assessed through the plots of weighted deviance residuals versus time. The Wald's χ^2-criterion evaluated the level of significance for each covariate. Patients were included in the statistical analysis according to the intention-to-treat approach. Analysis of variance for repeated measurements (MANOVA) was used to evaluate changes in the quality of life score during follow-up. All reported *P*-values are based on two-sided tests. SPSS 11 software (SPSS Inc., Illinois, USA) was used for all the statistical calculations.

RESULTS

Somatostatin receptors

The flowchart of study patients is shown in Figure 1. Octreoscan failed to demonstrate increased uptake of the radionuclear compound in the liver of 66 (52%) patients. In the remaining 61 (48%) cases, the scintigraphic findings were positive for overexpression of SSTR in the liver tissue (Figure 2). In 11 patients the whole body octreoscan visualized metastatic sites and in 5 of these cases provided additional detection sites to those of conventional imaging, previously unsuspected (bones, lymph nodes).

Therapeutic trial

Thirty one octreoscan positive patients were randomized to receive octreotide and 30 additional octreoscan positive patients (69.4 ± 1.17 years old, 22 men and 8 women) were to receive oral placebo-control group.

Of the octreotide group, a male patient-refused therapy. This patient was excluded from the study. Six patients, 2 men and 4 women, discontinued treatment from the third day, despite dose reduction (0.3 mg and 0.1 mg) because of severe diarrhea. The schedule to implement the modifications of octreotide dosage due to adverse effects was based on several consensus reports of the drug

Table 1 Descriptive characteristics of octreotide, control and SSTR-negative group

	SSTR-negative group	Control group	Octreotide group	*P*		
Number of patients	66	30	30		df	*P*
Age (yr)	69.4 ± 5.6	69.5 ± 5.6	69.4 ± 6.3	$F = 0.009$	125	> 0.05
Sex						
Male	36 (55%)	22 (73%)	20 (67%)	$\chi^2 = 3.45$	2	> 0.05
Etiology				$\chi^2 = 9.133$	4	> 0.05
HBV	38 (58%)	10 (33%)	10 (33%)			
HCV	26 (39%)	17 (57%)	19 (63%)			
HBV + HVC	2 (3%)	3 (10%)	1 (3%)			
Morphology				$\chi^2 = 0.842$	4	> 0.05
Multi nodular	13 (20%)	6 (20%)	7 (23%)			
Massive	45 (68%)	20 (67%)	21 (70%)			
Diffuse	8 (12%)	4 (13%)	2 (7%)			
AFP	3208 ± 4500	3096 ± 4500	2714 ± 5049	$F = 0.057$	125	> 0.05
Metastases	8 (12%)	7 (23%)	4 (13%)	$\chi^2 = 2.118$	2	> 0.05
Cirrhosis						
Stage B	32 (49%)	19 (63%)	15 (50%)	$\chi^2 = 1.91$	2	> 0.05
BCLC						
Stage C	56 (85%)	25 (83%)	25 (83%)	$\chi^2 = 0.054$	2	> 0.05

Table 2 Follow up of patients

	SSTR-negative group	Control group	Octreotide group	*P*
Number of events within 6 mo	25 (38%)	12 (40%)	6 (13%)	0.171
Number of events within 12 mo	65 (99%)	29 (97%)	21 (70%)	< 0.001
Number of events at the end of follow up	66 (100%)	30 (100%)	29 (97%)	1.000
Overall survival time (wk)	28; 21 to 33	28; 19 to 34	49; 28 to 72	< 0.0001

administration[40,41].

The remaining patients of this octreotide group (69 ± 1.2 years old, 17 men and 7 women) and all patients of the control group continued treatment until completion of the study.

The 66 patients with negative octreoscan (69.4 ± 0.7 years, 36 men and 30 women) formed the SSTR-negative group.

Table 1 shows the baseline characteristics of the patients. No statistically significant differences were observed as regards to the baseline characteristics of the participants. In particular, patients in all 3 groups were of similar age and had similar distribution of tumor morphology.

At the end of the follow-up period all patients, except one, had passed away. This patient died 4 wk later. The minimum and maximum follow-up interval was 8 and 160 wk, respectively. A significantly higher survival time was observed for the octreotide group (49 ± 6 wk) as compared to the control group (28 ± 1 wk) and to the SSTR negative group (28 ± 2 wk), LR = 20.39, df = 2, $P < 0.01$ (Table 2). This trend was also observed at six mo of follow up, but did not reach significant statistical value. No statistically significant differences were observed between the control and the SSTR-negative group regarding survival of our patients (Figure 3).

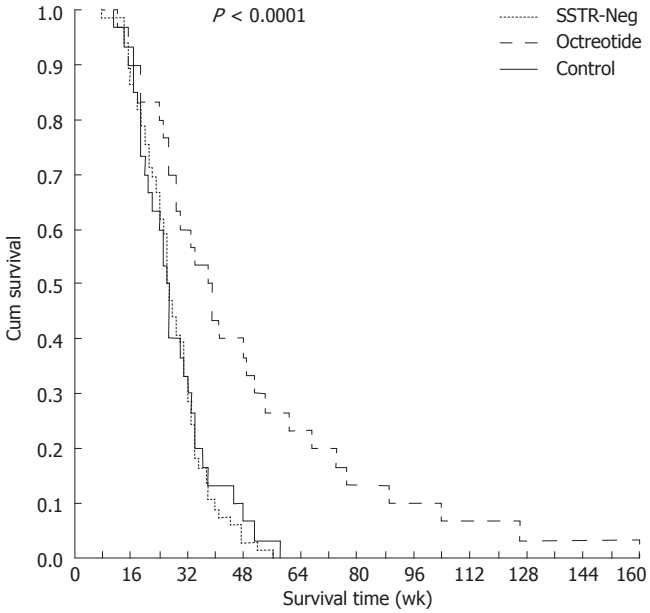

Figure 3 Survival probabilities in the groups of the study.

Using the Cox proportional hazard model, after controlling for age, sex, morphological characteristics of the tumor, etiology, metastases, cirrhosis stage, BCLC stage and AFP levels, we observed that patients in octreotide group had a 68.5% lower ratio (95% confidence interval 47.4%-81.2%, wild = 19.99, df = 1, $P < 0.01$), as compared to the SSTR-negative group, while patients in control group had a 7% lower hazard of death (95% confidence interval -30.8% to 15.5%, wild 0.570, df = 1, $P > 0.05$) as compared to the SSTR-negative group.

Quality of life ascertainment

A decreasing trend was observed in the QLQ-C30 score during the follow-up in all three groups of the study (Figure 4). During the first 12 mo of the follow up period

a 39% decrease was observed in control group, a 22% decrease in octreotide group and a 43% in the SSTR-negative group. Moreover, patients that had received octreotide presented significantly higher values of the QLQ-C30 score as compared to patients from the control group and SSTR-negative group (F = 125.9, df = 125, $P < 0.05$). The differences in the score were observed after the second mo of follow up.

There is no satisfactory volume of data on the quality of life of patients after the first year of follow-up. Thus, the statistical analysis of the QLQ-C30 questionnaire was based on the data of the first 12 mo.

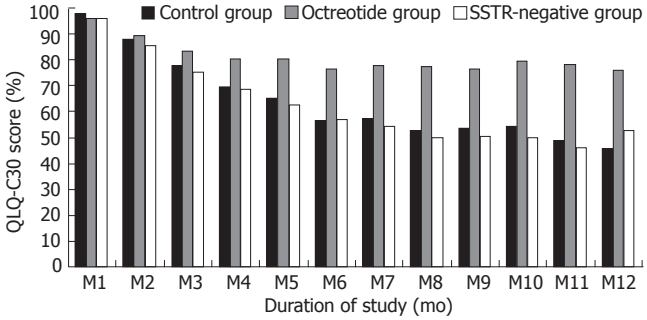

Figure 4 Score of the QLQ-C30 during the 12 mo of follow up.

DISCUSSION

Over the past few years a significant progress has been made in our understanding of the biology and functional significance of SSTR on human tumors. Based on these data, somatostatin and its synthetic analogues now play an important role in the management of gastrointestinal and pancreatic neuroendocrine tumors *via* peptide suppression. In addition, non neuroendocrine tumors may also be affected, but our knowledge in this field is still limited. However, important new data have recently been presented on SSTR-activated signal transduction pathways that are responsible for inhibition of cell growth and induction of apoptosis[42].

Human malignancies demonstrate a high degree of cellular heterogeneity and at different points in time (tumor progression). The growth of tumor cell clones that express neuroendocrine markers (e.g. SSTR, carcinoembryonic antigen, chromogranins), during the process of dedifferentiation, is a common feature of colon, breast and prostate cancer[43].

The overexpression of SSTR in human hepatocellular carcinoma cells has been verified[25] but the subtype(s) of SSTR that is overexpressed in the HCC tissue has not been adequately studied. Recently the presence of SSTR 2, 3 and 5 was demonstrated on the surface and in the cytoplasm of hepatic stellate cells isolated from an animal model[44].

In the present study, using SSTR scintigraphy, we demonstrated an increased uptake of radionuclear compound in the liver of 61 out of 127 patients (48%) with HCC and chronic viral liver disease. Our results are similar with the results of the study reported above. On the other hand, the used method is characterized by safety, mainly for cirrhotic patients with low platelet count and prolonged prothrombine time and reliability, especially for the detection of SSTR-2 that present a high affinity to octreotide[43,45]. Based on these data we administered, octreotide/octreotide long-acting formulation or oral placebo in a group of 60 patients, 30 and 30 in each group respectively, with advanced HCC and positive scintigraphic findings for SSTR.

Although TACE has shown to improve survival in well-selected candidates, only 12% of whole HCC population are suitable for this treatment modality. Patients with well-preserved liver function and multinodular tumor without vascular invasion seem to be the best target population[46]. From our study population, only 7 patients (5.5%) can be considered suitable for TACE, a percentage very low for a therapeutic option without predetermined benefits.

Furthermore, another group of 66 patients with HCC, but with negative scintigraphic findings was followed-up in the same manner.

The performed statistical analysis revealed a significant difference regarding survival between the octreotide and the two other groups ($P < 0.001$). Between the control and the SSTR-negative group no statistically significant difference ($P = 0.450$) was observed and this similar prognosis probably suggest that the presence of SSTR in the tumor does not mark its aggressiveness. Recently, Yuen *et al*[35] reported that octreotide long acting formulation treatment was not effective in prolonging survival in patients with advanced HCC. In this study the presence of SSTR in the tumor was unknown and the administration of octreotide probably was uneffective at a percentage higher than 50% of patients[25]. On the other hand, nearly half of the patients had portal vein thrombosis, a statistically significant factor for diminished survival in HCC patients[47]. The high percentage of patients (37.1%) dying before receiving the first injection of octreotide long acting formulation, two wk after randomization, also indicates an aggressive disease in the Yuen study population. Furthermore, in this study, in a percentage greater than 80% of patients, the main causative factor of HCC and the underlying cirrhosis was HBV infection, a fact that can be another possible explanation for the poor survival rates. Although no significant differences in survival according to viral etiology in Western European cirrhotic and HCC patients are reported[48-50], further studies are required to determine whether the survival in Caucasian and East Asian HCC populations are influenced by the viral loads and genotypes, the serologic viral markers, dietary habits and the expression of SSTR.

Despite the reports for normalization of AFP levels and regression of the tumor size due to somatostatin analogues treatment[33,51,52], no AFP reduction and decrease of the tumor mass or the number of the satellite sites were observed in our patients. The statistically significant survival benefit for the octreotide group can probably be explained due to a slower tumor progression. Inhibition of proliferation and induction of apoptosis of HCC cells have been reported by *in vitro* studies[22,26,51,53-55].The inhibitory effect of octreotide on angiogenesis must also be considered[27,56]. In the present study, octreotide long acting formulation also showed to improve the quality of life of

the treated patients significantly as compared with that of patients from the two other groups and the difference in the QLQ-C30 score observed after the second mo of follow-up. Although the experience with somatostatin analogues treatment in HCC patients is limited, our results are in agreement with previous reports[33,52].

Together with the prolongation of survival, the quality of life is considered as one of the main endpoints for any palliative treatment in cancer patients. Unfortunately, for patients with advanced HCC there is not an established palliative treatment yet with respect to these two parameters.

The proposed therapeutic approach has shown to improve survival and the quality of life in SSTR positive patients with advanced HCC and, despite the high cost, it seems to be an attractive therapeutic option for those who have no possibility for other therapeutic modalities such as liver transplantation, surgical resection, PEI or TACE.

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