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ORIGINAL ARTICLE

Selective hepatic arterial infusion of In-111-DTPA-Phe[1]-octreotide in neuroendocrine liver metastases

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Abstract
Purpose The aim of this study is to evaluate the effectiveness of ^{111}In-DTPA-Phe[1]-octreotide infusions after selective catheterization of the hepatic artery in inoperable metastasised liver, sst_2 receptor-positive neuroendocrine tumours due to the effect of ^{111}In Auger electron emission, minimising in parallel the toxicity of non-target tissue.
Methods The average dose per session administered monthly to each patient (17 cases in total) was 6.3±2.3 GBq. Repetitions did not exceed 12-fold, except in one case (15 sessions). Response assessment was classified according to the Response Evaluating Criteria in Solid Tumours. CT/MRI scans were performed as baseline before, during and after the end of treatment, and monthly ultrasound images for follow-up measurements. Toxicity (World Health Organization criteria) was measured using blood and urine tests of renal, hepatic and bone marrow function.
Results Complete response was achieved in one (5.9%) patient and partial in eight (47.0%), and disease stabilization in 3 (17.7%) patients; five (29.4%) did not respond. A 32-month median survival time was estimated in 12 (70.5%). Nine of these 12 surviving had a mean target diameter shrinkage from 144±81 to 60±59 mm. Grade 1 erythro-, leuko- and thrombo-cytopenia occurred in three (17.6%) cases.
Conclusion In unresectable metastatic liver lesions positive for somatostatin receptors repeated, transhepatic high doses of ^{111}In-DTPA-Phe[1]-octreotide show an effective therapeutic outcome. Given the locoregional modality character of the administration technique plus the extremely short range of ^{111}In Auger and internal conversion electrons emission, no nephro-, liver- or myelo-toxicity has so far been observed.

Keywords ^{111}In-DTPA-D-Phe1-octreotide · Therapeutic infusions · Hepatic artery catheterization

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Introduction

The somatostatin analog octreotide binds with high affinity to the most frequently expressed somatostatin receptor subtype sst2 in the majority of the neuroendocrine tumours [1, 2]. Labelled with indium 111 (Octreoscan, Mallinckrodt, Petten, The Netherlands), which emits γ-photons of two energies (172 and 245 keV) [3] as well Auger and internal conversion electrons, it was initially used for diagnostic purposes. After i.v. application, Octreoscan is internalized into the tumor cell by fluid-phase endocytosis and degraded in two insoluble metabolites ^{111}In-DTPA-D-Phe-Cys-OH and ^{111}In-DTPA-D-Phe-OH [4–6] inside the lysosomes, close to the nucleus, where they are retained [2, 4]; the empty receptor drives again to the cell membrane surface.

First, in 1993, high doses of In-111-DTPA-Phe[1]-octreotide were used for the treatment of these type of tumours [3,

7] via antecubital intravenous infusions exploiting the Auger and internal conversion electron emission of indium 111 [3, 8, 9]. Typical cellular diameters vary from 6 to 20 μm with the corresponding diameters of the cell nucleus ranging from 4 to 18 μm (Fig. 1); this obviously means that DNA lies within the destroying range of Auger (<1 μm) and internal conversion electrons (200–550 μm) [10, 11]. Taking into account that in every In-111 decay a spontaneous emission of 14.7 Auger electrons results, thus enabling it to destroy few numbers of cells, only small- and medium-size nodules and in repeated mode could be candidates for this type of therapy [12]. This therapeutic modality aimed at destroying the tumour tissue invasively through the 4–26 keV/μm linear energy transfer delivered from these electrons [13]. The disadvantage of the procedure was the increased retention of the radiolabel in the kidneys that are considered to be the critical organs [14, 15].

To maximize the absorption of activity onto the metastatic liver lesions, achieving a larger destruction with the lowest possible delivered dose to the kidneys, it was decided to modify the mode of administration by applying radioactivity as close as possible to the malignancy after selective catheterization of the hepatic artery [16]. The purpose of this study was to assess and evaluate the effectiveness of the procedure in non-resectable liver neuroendocrine metastases, in long-term, minimizing in parallel the toxicity to the non-target tissue.

Materials and methods

Patients

Seventeen *selected* patients (14 men, three women; mean age, 59 years; age range, 26 to 70 years) with *non-operable* neuroendocrine liver metastases confirmed by biopsy received per monthly session 4,070–7,030 MBq of In-111 incorporated in 40 to 50 μg DTPA-Phe[1]-octreotide after selective hepatic catheterization; the dose range was markedly large due to the variability among catheterization and delivery day, resulting in a dose manipulation according to the tumour size. All patients were in *advanced stage* and *progressive disease*, without having any other conventional treatment options (chemotherapy and/or radiotherapy). The liver metastases originated from the lungs (carcinoids, n=5), head of the pancreas (neuroendocrine tumours, n=8), small intestine (carcinoids, n=3) and colorectal area (paraganglioma, n=1). None of them had extrahepatic metastases. Before commencement of the study, the protocol was approved by the Institutional Committee on Human Investigation of the Aretaieion University Hospital of Athens, Greece. An informed consent form was signed by each patient before the enrolment to the procedure.

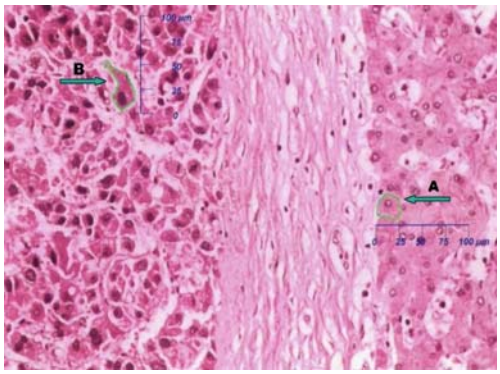

Fig. 1 Schematic representation of two scales (*in blue*) superimposed on a histologic sample of normal (*A*) and tumor liver cells (*B*). Cellular membrane is delineated by *green line*. Nuclei of normal and tumor cells are well distinguished. Comparing cell dimensions and distances between cell surface and nuclei obviously can be elicited that DNA lies within the micrometer range of In-111 emissions

A diagnostic Octreoscan was initially performed on all patients (eligibility criterion: a 130% uptake in the tumour compared to liver, grade 4, according to a visual score; [17, 18], EANM's Guidelines issued on September 2, 2003; the latter was estimated from regions of interest, ROIs, drawn on tumour and normal liver parenchyma, allowing us to proceed with therapeutic applications). Patients showing a radiopharmaceutical tumour uptake less than 130% compared to the surrounding normal liver parenchyma, a Karnofsky Index less than 30, and thus, a poor life expectancy, a platelet count less than 70 cells$\times 10^9$/l and a serum creatinine higher than 1.2 mg % were excluded from the study. Patients with a Karnovsky of 30–70 did not perform any worse, so this category of patients were also included. Thus, eligibility for the trial was predominately on the basis of a grade 4 Octreoscan visual score. Before the initialization of the therapy routine haematology, liver and kidney function tests, the serum tumour marker chromogranin-A (Cr-A) and hormone levels [serum gastrin and insulin, ACTH and serotonin, and 24 h urinary free catecholamines and 5-hydroxyindoloacetic acid (5-HIAA)] were determined and repeated on a bi-monthly basis; the consistency of the intrahepatic tumour tissue was estimated according to the ultrasound (US), CT or MRI findings. Renal, hepatic and bone marrow toxicity was assessed using World Health Organization criteria. Twelve out of 17 patients on repeatable long-acting somatostatin analogue (Sandostatin-LAR, Novartis, Basle, Switzerland) in a dosage of 30 mg per 20 days i.m. did not discontinue this drug. Amino-acids co-infusion was not applied, as no renal toxicity could be expected with In-111-DTPA Phe[1]-octreotide [19].

Equipment and procedure

Selective hepatic angiography was conducted with a digital angiographic unit (Optimus, Phillips, The Netherlands). A

5.0-F valved sheath (Introducer II-long sheath; Terumo; Tokyo, Japan) was inserted into the femoral artery with the patient under local anaesthesia, which was induced by injecting 10 ml of 2% lidocaine subcutaneously (Xylocaine; Astra, Sweden). After obtaining arterial access, a diagnostic visceral arteriogram was performed to delineate the arterial supply to the tumour, determine the presence of variant arterial anatomy and confirm portal vein patency, even though portal vein thrombosis does not necessarily constitute a contra-indication to perform trans-catheter arterial radionuclide infusion. Celiac and superior mesenteric arteriography was performed with a Cobra II 5.0-F catheter (Glidecath; Terumo, Japan), which was advanced into the proper hepatic artery by using a 0.035-in. gliding guide wire (Guide Wire M; Terumo, Japan). The catheter was then selectively inserted into either the right or left hepatic artery or in turn to both hepatic artery branches dependent on the tumour intra-hepatic location. The size and location of the neuroendocrine nodules were assessed using the Couinaud nomenclature [20], according to which the liver is divided into eight independent segments, each of which has its own vascular inflow, outflow and biliary drainage. Tumour size and location were evaluated by means of a consensus between two observers who compared the images obtained. Having safely positioned the catheter within the nearest artery to the tumour, intra-hepatic radionuclide infusion followed.

Intrahepatic infusion In patients where arterial anatomy variants were noted, the dose was divided and administered consecutively as previously prescribed. Neither of the treated patients had any extrahepatic metastases. In-111-DTPA-Phe^1-octreotide solution (Octreoscan, Mallinckrodt) covered by a 0.787-in.-thick lead shield was injected by a nuclear physician slowly and carefully within a time duration of 6 to 8 min. At the end of the procedure, a 10-ml saline flush was given to deplete the remaining radioactivity on the catheter walls. After the end of the infusion, a stopcock heparinised catheter was inserted antecubitally to drain blood samples 10 and 20 min, and 2, 5, and 24 h post-catheterization for dosimetric calculations. For the same reasons, 24-h urine was collected.

Patients had to stay hospitalised for 48 h in a single bedroom, with its own toilet dedicated for radionuclide-treated patients. At the time of discharge, patients were briefed to constrain the doses received by the members of the public and the close family taking into account the dose rate (mSv/h) at 1-m distance from the patient's body.

Dosimetry assessment

After ^{111}In-DTPA-Phe^1-octreotide infusion, planar images were obtained using a large field of view camera equipped with a parallel-hole collimator. Anterior and posterior whole-body scintigrams were taken just after the catheterisation as well as 24 and 48 h post infusion. Radioactivity bio-distribution was evaluated by calculating the geometric mean of the anterior and posterior counts in ROIs drawn over the major organs [21]. Parts of the organs showing tumour infiltration or organ-overlapping were excluded from the activity uptake evaluation study; these were included in the assumptions made, and time–activity curves were created consequently from each ROI (anterior and posterior view). Blood samples were collected 30 min and 2, 4, 8, 24 and 48 h p.i. to calculate the residence time in blood and, in consequence, the red marrow residence time (MIRD pamphlet no. 11). Twenty four hours of urine samples were collected to calculate the kidney excretion capability and the biological excretion half time (MIRD pamphlet no. 16). Based on the bio-distribution data, (a) the residence times of the tumour and the critical organs as well as (b) the absorbed dose per unit of cumulated activity, S values were calculated using the Monte Carlo method (version MNCP-4D). For this purpose, three male and three female adult mathematical models of different heights were designed and constructed according to Kontogeorgakos et al. [22]. Three different MC runs were performed for each target organ. In the first run, the primary photons were simulated, whereas in the second and third, the Auger and IC electrons, respectively, according to the Indium-111 spectrum. Tumor S values were calculated for spherical lesions of different diameters consisting of soft tissue with a 1.04 g/cm3 density with the assumption of a uniform radiopharmaceutical distribution and taking into account that the source was the only target organ.

Post-treatment and follow-up studies

The aforementioned radionuclide hepatic infusion was repeated 4 to 5 weeks apart, with a goal of administering 12 doses; the same modality was applied for all patients except in one case where the sessions have been increased to 15. Initially, before the commencement of the treatment, CT and/or MRI scans and US imaging were performed and have been considered as the baseline of the pre-therapy lesion status. US was repeated monthly just before the beginning of each session and was the main tool of the follow-up estimation. A second CT or MRI scan was performed at the end of the entire therapy scheme. Response to the treatment procedure was measured according to the Response Evaluating Criteria in Solid Tumours (RECIST) criteria, taking into account a maximum of five measurable lesions in the liver as target lesions: complete response (disappearance of all target lesions), partial response (at least a 30% decrease in the sum of the longest tumour diameter), progressive disease (at least a 20%

increase in the sum of the longest diameter), stable disease (neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum of the longest diameter since the treatment started) [23].

Routine measurement of complete blood count, liver and kidney function tests, the serum tumour marker chromogranin-A (Cr-A) and hormone levels as previously described were measured before each session and at follow-up visits. CT images, non-enhanced as well as contrast-enhanced CT images (5-mm slice thickness, 1.50 pitch, 120 kVp, 220–250 mAs), were performed with model PQ 6000 (Picker International, Highland Heights, OH, USA) and Hi-Speed Advantage (GE Medical Systems, Milwauckee, WI, USA) spiral scanners.

MR tomoscans MR images were obtained by using a 1.5-T Magnetom Vision Unit (Siemens) and two pulse sequences: T2-weighted turbo spin echo [4,200/83 or 165 (repetition time millisecond per echo time millisecond), 7-mm slice thickness, 128×256 matrix, 3-min imaging time) and T1-weighted gradient echo with a fast low-angle shot technique (174.9/4.1, 80° flip angle, 7-mm section thickness, 128×256 matrix, 22-second imaging time).

US tomoscans The US scans were acquired in the sagittal, transverse and intercostal planes by using ATL 3000-HDI (Advanced Technology Laboratories, Bothell, WA, USA) and AU 590 (Esaote Biomedica, Genoa, Italy) units and a convex 4–2 MHz probe.

Statistical analysis

For the assessment of the treatment efficiency, nodule size and number were compared before and after the end of the therapy according to the RECIST criteria as previously described [23]. All statistics were calculated using the MedCalc 9.1 for Windows software. For the statistical comparison of the number of nodules and their diameter, the Wilcoxon test was employed. Kaplan–Meiers survival analysis was applied for the estimation of the treatment efficiency.

Results

A total of 180 infusions of In-111-DTPA-Phe^1-octreotide were administered by hepatic artery catheterisation (Table 1). The mean number of treatments applied per patient was 11 (range, 3–15), and the mean level of radiation activity delivered per In-111-DTPA-Phe^1-octreotide dose was 58 GBq (range, 13–77 GBq). No pain was noticed, except for some abdominal discomfort in almost all patients, temporary chest and head rush in five and blood pressure drop (from 140 to 9 mmHg) in 3 during the infusion procedure, as well as vomit and diarrhoea at the first day p.i. The mentioned side effects disappeared shortly thereafter without any specific medical intervention.

Patient no. 11 who died suddenly due to reasons not related to the primary disease received the lowest total activity (13 GBq); patient no. 6 who suffered from pancreatic carcinoid received the highest dose, resulting in a marked reduce for both tumour size and nodule number. The median follow-up period was 31 months. For patient no. 5 with removed pancreatic carcinoid, a complete response was achieved, confirmed by MRI (Fig. 2). In eight patients (nos. 1–3, 6–9 and 14) suffering from carcinoids of different origins, there was a partial response with a significant reduction of the tumour diameter (p= 0.1124). Three patients (nos. 10, 12 and 13) attained disease stability 15.3 mo after the last treatment. A further five patients (nos. 4, 11 and 15–17) died 4.4 mo after their last therapy.

No evidence of treatment-associated toxicity was noticed in seven out of 17 patients during this trial as well as 32 months after the last radionuclide treatment. In five patients just after the transhepatic infusion, a transient chest and head\rush, lasting about 20 min, was depicted. In three patients, nausea and vomiting within the first 24 h p.i. was present, whereas six complained of temporary slight abdominal discomfort. WHO toxicity grade 1 anaemia occurred in five and grade 1 leucocytopenia and thrombocytopenia in three. Serum creatinine, transaminases and alkalic phosphatase did not change at all in the entire group treated. Regarding the hormone figure levels, no abnormal values have been depicted throughout the whole study, and as far as the 12-patient group under repeatable Sandostatin–LAR therapy, no differences have been observed concerning the response outcome.

In reverse, a clear decrease on serum Cr-A was observed in partial and complete responders, whereas in progressively responding cases, a marked increase was shown (Fig. 3). Four out of the six deaths recorded were related to the main tumour disease, one resulted due to a second primary cancer originating from the stomach and another to a heart attack.

The remaining nodules at the end of the follow-up were fewer as compared to those at the beginning (1.83, SD= 1.11 and 3.75, SD=1.36, respectively, p=0.0032. No overlap between the confidence intervals of the two means can be seen in Table 2, suggesting that this difference supports our claim of the treatment efficacy.

The total diameter of the remaining nodules at the end of the follow-up (Table 3) was smaller than those at the beginning of the therapy but not significant (90.10, SD= 78.26 and 143.58, SD=70.68, respectively, p=0.1124).

Table 1 Patient characteristics and therapy outcome

Patient no.	Patient/ sex	Age (years)	Tumor histotype/ primary origin	No. of sessions	Total activity (GBq)	No. of initial nodules/ total diameter(mm)	No. of final nodules/total diameter	Response
1	PA/m	63	Carcinoid/small intestine	12	70	5/110	3/72	Partial
2	BA/f	53	Carcinoid/lung	12	69	5/80	2/30	Partial
3	PD/m	62	Carcinoid/pancreas	12	51	4/195	2/90	Partial
4	S A/m	69	Carcinoid/lung	15	65	Non-measurable disease	Minimal degeneration	Progression/ death
5	SB/f	55	Carcinoid/pancreas	12	68	5/200	0/0	Complete
6	AK/m	48	Carcinoid/pancreas	12	77	3/60	1/11	Partial
7	PK/m	26	Carcinoid/pancreas	12	63	5/65	0	Partial[a]
8	SP/m	68	Carcinoid/small intestine	12	71	5/230	3/120	Partial
9	DA/m	67	Carcinoid/lung	12	70	4/275	3/172	Partial
10	AT/m	70	Carcinoid/small intestine	12	68	Non measurable disease	Minimal degeneration	Stable
11	BC/m	65	Carcinoid/pancreas	3	13	2/170	2/210	Progression/ death
12	KS/m	69	Carcinoid/pancreas	12	60	Non-measurable disease	Degeneration	Stable
13	DI/m	46	Rectal paragaglioma	12	58	3/108	2/108	Stable
14	PI/m	56	Carcinoid/lung	12	70	3/80	3/48	Partial
15	KE/m	74	Carcinoid/pancreas	6	41	1/150	1/220	Progression/ death
16	KA/f	70	Carcinoid/lung	5	28	Non-measurable disease	Minimal degeneration	Progression/ death
17	GG/m	28	Carcinoid/pancreas	6	35	Non-measurable disease	Minimal degeneration	Progression/ death

[a] The case is considered as partial responding because the primary lesion in pancreas is inoperable; degeneration, change in Echo pattern on non-measurable disease; stable disease, not classifying for PD or PR; total diameter: the sum of the longest tumor diameters.
m male, *f* female

Figure 4 is an illustration of a Kaplan–Meier survival probability (%) of CR + PR group vs SD and PD cases. The graph shows a statistically significant long follow-up with a median survival time of 32 months (p=0.73) without any tumour recurrence up to date.

Figure 5 represents the patients response to the therapy (%) related to the tumor average dose (Gy) where the highest response was observed at an absorbed dose level around 700 Gy (around the seventh session).

Figure 6 displays the therapeutic effects (response %) regarding the tumour size (average diameter in millimeter per nodule number), and Fig. 7 illustrates the diameter shrinkage (%) vs the delivered dose to the tumour (GBq) that denotes a visible cut-off value at ≈41 GBq.

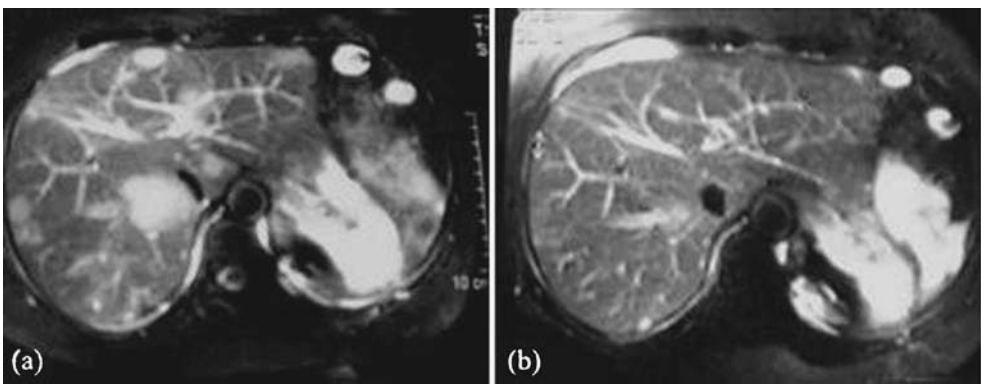

Fig. 2 Multiple liver metastases from a small intestine carcinoid in a 55 year-old woman. **a** Axial MRI (T2-weighted turbo spin echo) scan before selective catheterization of the hepatic artery (SCHA) and radionuclide infusions show multiple hepatic metastases; **b** axial MRI (T_2W) scan obtained 8 months after SCHA and radionuclide infusions of In-111 shows almost complete disappearance of the metastatic lesions

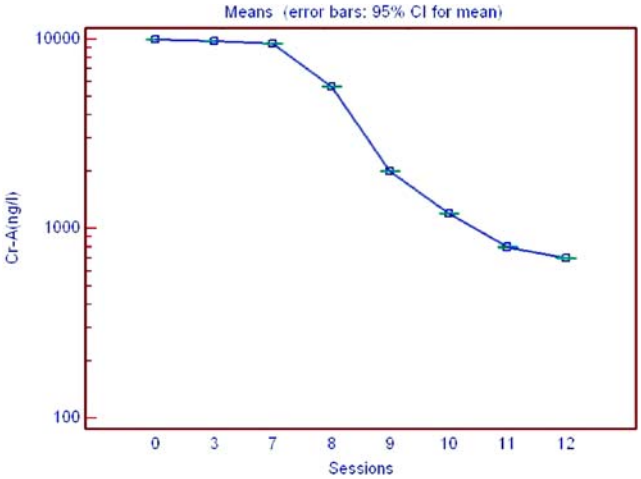

Fig. 3 Serum tumour marker chromogranin-A levels vs a 12th-month outplan for partial and complete responding patients. During treatment and follow-up, a marked decrease in serum chromogranin-A levels had occurred for PR/CR patients (mind the log scale)

Dosimetry

The organ average radiation dose estimation after ^{111}In-DTPA-Phe^{1}-octreotide transhepatic infusion was found as follows: (a) liver tumor, 10.8 mGy/MBq; (b) liver, 0.14 mGy/MBq; (c) kidneys, 0.41 mGy/MBq; (d) spleen, 1.4 mGy/MBq; (e) pancreas, 0.13 mGy/MBq; and (f) bone marrow, 0.0035 mGy/MBq. The average absorbed dose per session to a tumour for a spherical mass of 10 g was estimated to be 10.8 mGy/MBq, depending on the histotype of the tumour [21, 24].

Discussion

Treatment modalities against liver neuroendocrine metastases can be categorized as invasive (surgical resection [25, 26]), minimally invasive (selective transarterial (chemo) embolisation [27] and radiofrequency ablation [28]) and systematic [15, 29–33]. All these techniques, while promising, still have certain limitations and need to be tested

Table 2 Mean number of the initial and remaining nodules at the end of the entire therapeutic scheme

	N	Mean	SD	95% CI	SDE
Initial Diameter	12	143.58	70.68	98.68–188.498	20.40
Final Diameter	12	90.10	78.26	40.36–139.81	22.59
P value	0.112				

N no. of patients, *SD* standard deviation, *95% CI* a 95% confidence interval for the arithmetic mean, i.e. the range of values that contains the true population mean with probability 95%, *SDE (standard error)* the standard deviation of the sampling distribution of the statistic

Table 3 Mean diameter of the initial and remaining nodules at the end of the entire therapeutic scheme

	N	Mean	SD	95% CI	SDE
No. of initial nodules	12	3.75	1.36	2.89–4.61	0.36
No. of remaining nodules	12	1.83	1.11	1.12–2.54	0.60
P value	0.0032				

N no. of patients, *SD* standard deviation, *95% CI* a 95% confidence interval for the arithmetic mean, i.e. the range of values that contains the true population mean with probability 95%, *SDE (standard error)* the standard deviation of the sampling distribution of the statistic

prospectively in a larger group of patients. Recently, indium-111- [17], yttrium-90- [34–36] and/or luthetium-177-labelled [37] peptides have been applied as a new alternative therapeutic option to confront these type of tumors.

Trials using In-111 pentetreotide in therapeutic schemes have been conducted in our institution after selective catheterisation of the hepatic artery since 1997 [16], whereas antecubitally via i.v. infusions had been reported by other investigators [17, 38, 39] (Table 4). In our series, nine out of 17 patients (52.9%) showed one complete and eight partial response; three (17.7%) had a stable disease, whereas in five (29.4%), the disease progressed, the therapy was discontinued and they died shortly thereafter (Table 1). In consequence, 70.6% of the patients showed some radiological benefit from the treatment. Compared to the aforementioned authors working with In-111 octreotide [17, 38, 39], we observe the highest objective response (52.9%) vs 43% of Valkema et al. (nine of 21 patients), 31% of

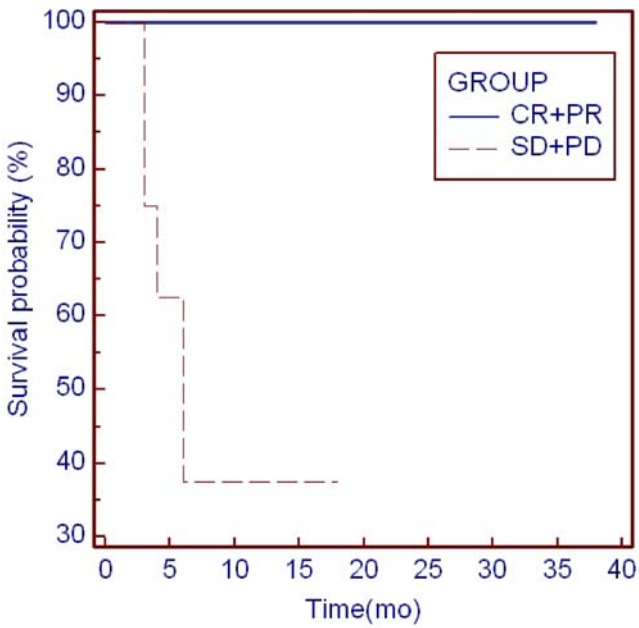

Fig. 4 Kaplan–Meier survival probability (%) of CR + PR group vs SD and PD cases (median survival 32 months; p=0.73)

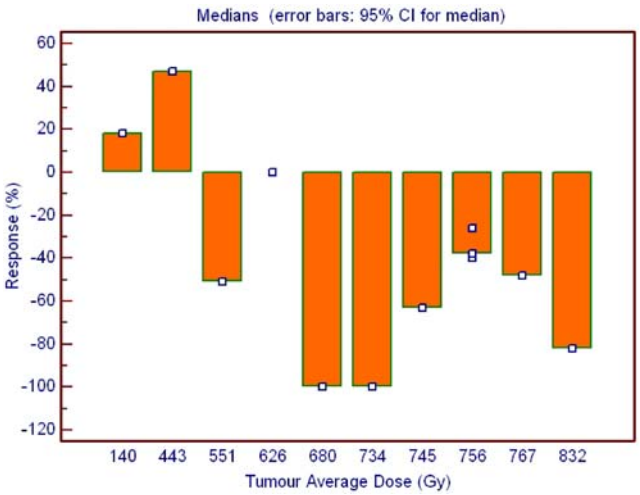

Fig. 5 Dosimetric data of tumour average dose (Gy) vs response of therapy (%). Graph suggests that the resultant critical point must be estimated around 700 Gy

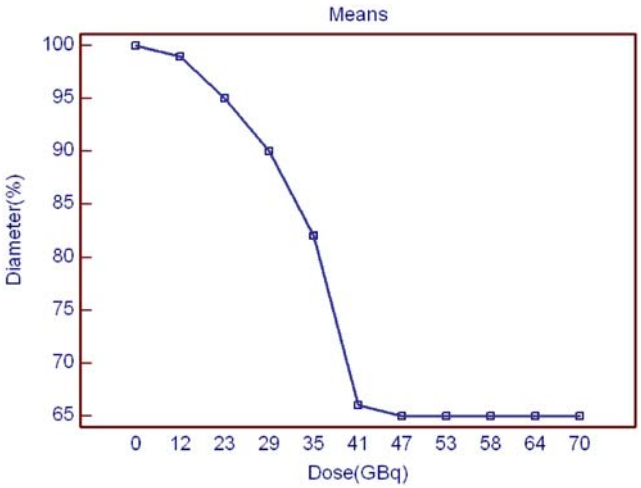

Fig. 7 The diameter shrinkage (%) vs the delivered dose to the tumour (GBq). Graph is clearly indicating a cut-off value for tumour response at ≈41 GBq

Buscombe et al. (five of 16 patients), 7.7% of Anthony et al. (two of 26 patients) but the lowest disease stabilization (17.7%) vs 24% of Valkema et al. (five of 21 patients), 44% of Buscombe et al. (seven of 16 patients) and 81% of Anthony et al. (21 of 26 patients). This might be explained due to the different application way, where the mean absorbed dose per session by the tumor is estimated to be markedly higher (Table 4) compared to applications given i.v. by Förster et al. and by Helish et al. [40, 41]. Some differences are observed regarding the non-responders, i.e. 29% (five patients) as far as our cohort and 33% (seven patients), 25% (four patients) and 11.3% (three patients) as far that of Valkema et al., Buscombe et al. and Anthony et al., respectively. In our study, the overall median survival time of 32 months (Fig. 4) was greater compared to the 18 months reported by Anthony et al. and to the 9 months referred by Buscombe et al. These differences might be caused by the different patients' profile as the size and number of tumours, the existence or not of the primary lesion and the receptor density that make the comparison difficult. The 4.3-month mean time interval in our cases between progression and death due to the disease was identical to the 5 months reported by Buscombe et al.

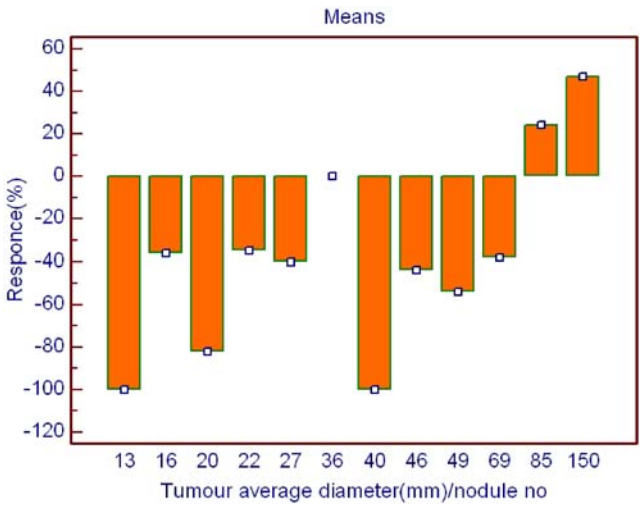

Fig. 6 The therapeutic effects (response %) regarding tumour size (average diameter in mm per nodule number). Graph is indicating that the optimal tumour regression values were achieved in patients with a median value of tumour diameter in millimeter per nodule number equal to 38, whereas in contrast for large values of the latter, there is no reduction observed (Wilcoxon test (paired samples): median value of tumour diameter in millimeter per nodule number=38, p=0.0005)

The use of the carrier molecule pentetreotide, a somatostatin analog that binds with affinity to cell-surface somatostatin receptor subtype 2, subtype 3 and subtype 5, implies that the therapeutic radioisotope selected must have a suitable path length to reach the DNA of the nucleus and cause cell death. The length as well as the energy of Auger and internal conversion electrons of ^{111}In emission is not ideal. They have a particle range that cannot exceed two to three cell diameter and do not facilitate crossfire between adjacent cells. Additionally, their (0.5 to 25 keV for Auger and 145 to 245 keV for internal conversion electrons) energy is poor compared to that of the β-emitters ^{90}Y and/or ^{177}Lu. However, these phenomenically ^{111}In emission limitations have their benefits: (a) Comparing the signif-

Table 4 Tumour-absorbed dose comparison between i.v. and i.a. administration of In-111 octreotide

Organ	i.v. infusion, Förster et al. [40]	i.v. infusion Helisch et al. [41]	i.a. infusion, our study
Liver dose (mGy/MBq)	0.59	0.50	0.14
Tumor dose/ liver dose	6.27	21.10	77.14

icance of the *S* values for the Auger and internal conversion electron emitters used by the aforementioned investigators, ^{111}In has an impressive high dose [42] that justifies its cellular damage efficiency; (b) regarding a possible nephro-, liver- or myelo-toxicity that hardly deals all previous investigators (Table 5, [17, 18, 38, 40, 41]) in practice do not affect ^{111}In treatment.

We speculate on Auger and internal conversion electron emission of the element indium-111. In fact, Auger electrons RBE is the dominant component responsible for the DNA catastrophe, whereas the support of the internal conversion electron emission is of a much lower importance. Additionally, Coster–Kroning and super-Coster–Kroning electrons might also have participation but is generally neglected. All the emissions mentioned are bibliographically reported as Auger electron emissions under the large umbrella of the Auger electron therapeutic effectiveness without being separately nominated [43]. Furthermore, by thorough observation of Indium's-111 decay mode [44], the two 171- and 245-keV gamma emissions cover a 0.902 and a 0.940 frequency, respectively, that are not to be ignored. In consequence, we can conclude that a great degree of indium-111 RBE deals with the gamma radiobiological tissue burden, too. The DNA chain-destroy owes its damage to all mentioned gammas and Auger electrons emission.

As far as hepato-toxicity according to our dosimetric measurements (Table 5, [45–49]), the liver does not receive as much activity as it might be assumed and expected. This is directly related to the administration route, as the radiopharmaceutical first pass enters the feeding tumour arterial net and is binded by tumour somatostatin receptors, resulting in a lower absorbed activity rate compared to that calculated after an i.v. infusion.

Concerning a possible nephrotoxicity, recent investigations by de Jong [50] proved that the concentration of the radiopharmaceutical is found to be in the inner zone of the cortex, whereas the sensible to the radiation glomeruli are situated in the outer one; hence, ^{111}In electron emission might not practically reach them. So far, no patient has developed any grade of renal toxicity up to date according to the latest follow-up data.

The disadvantage of administering i.v. long-lived radionuclides for therapy lies in the fact that a substantial dose proportion is dissipated within the systematic circulation and hence a reduced dose impact reaches the target. On the

Table 5 Comparative WHO toxicity and dosimetry data with In-111, Y-90 and Lu-177 radiolabelled somatostatin analogs

Authors	WHO Toxicity Criteria grade				Dosimetry			Response WHO Criteria		
	Ligand	Hematologic grade/adm %	Renal	Liver	Kidney dose (mGy/MBq)	Liver dose (mGy/MBq)	Tumour lesion/ liver ratio	CR	PR	SD
Foerster et al. [40] i.v. adm	In-111 octreotide	nr	nr	nr	nr	0.59	6.27	nr	nr	nr
Helisch et al. [41] i.v. adm	In-111 octreotide	nr	nr	nr	1.98	0.40	9.42	nr	nr	nr
Limouris et al. [45] i.a. adm	In-111 octreotide	1	nr	nr	0.41	0.14	77.14	6	47	18
Valkema et al. [17] i.v. adm	In-111 octreotide	3–4	1 (2%)	nr	0.46	nr	nr	0	33	67
Anthony et al. [38] i.v. adm	In-111 octreotide	3–4	1	3	nr	nr	nr	0	8	81
Cremonesi et al. [49] i.v. adm	In-111 octreotide	nr	nr	nr	(0.12–0.91)	0.05–0.24	(0.7–30.5) / (0.05–0.24)	nr	nr	nr
Bodei et al. [47] i.v. adm	Y-90 DOTA	3–4 (43%)	Amino-acids	nr	3.4	0.83	nr	2	18	45
Helisch et al. [41] i.v. adm	Y-90 DOTA	nr	nr	nr	1.71	0.72	8.97	nr	nr	nr
Waldherr et al. [48] i.v. adm	Y-90 DOTA	3 (3%)	2 (3%)	nr	nr	nr	nr	2	22	61
Kwekkboom et al. [18] i.v. adm	Lu-177 DOTA	3 (1%)	nr	nr	nr	nr	nr	3	35	41
Kwekkboom et al. [46] i.v. adm	Lu-177 DOTA	3–4 (<2%)	nr	nr	nr	nr	nr	2	26	35

nr not referred

other hand, administering the dose intra-arterially after selective catheterisation of the hepatic artery as close as the liver metastases, a higher concentration percentage is expected to reach the tumour, and consequently, a higher delivered dose and tumour destroy. Studying thoroughly Fig. 5, the seventh session has been defined as the critical turning point, estimated at around 700 GBq cumulative administered activity. From 0 up to 700 GBq, there is not any real tumour decrease (either in nodule numbers or in diameter length). This 'inertia' time indicates an argument to consider further treatment after six therapies, at least to achieve obvious response results. It is certainly worth mentioning that two of 17 patients, six and seven underwent surgery, 4 and 9 mo post-therapy, respectively. This might be an interesting neo-adjuvant modality as a benefit for the remaining resistant nodules; the latter preventing to a degree the metastatic tendency, as nodules are solid but necrotic.

Furthermore, according to our findings, the average absorbed dose after transarterial administration of 63.1 GBq delivers 681.6 Grays for the tumor, 25.9 Grays for the kidneys, 8.8 Grays for the liver parenchyma, 87.0 Grays for the spleen and 0.22 Grays for bone marrow. Concerning the renal-tolerated dose, it has been estimated at 25–27 Grays; the latter deals with external beam irradiation delivered in both kidneys, having a 5% probability of late toxicity within 5 years (tolerated dose, 5:5). In contrast, radionuclide delivery by transarterial infusions is a continuous, non-fractionated, dose–rate repetitive radiotherapy. All that implies that comparison between these two modalities (i.v. vs i.a.) with such basic different characteristics should be cautious.

Apart from the sum of the longest diameter for all target lesions (RECIST criteria), the response to the treatment shown in our investigation is highly related to another parameter, that being of the average tumour size (the longest diameter divided to the number of nodules). As we can observe, (a) three out of five (60%; non-measurable disease) cases of our cohort (patients nos. 4, 16 and 17) died, even though they showed some responding signs (i.e. degeneration) ultrasonographically [45], while the two remain in stable disease status of unpredictable morbidity fate; (b) in the 12 (measurable disease, md)-patient group, only two died without completing the treatment, both presented with large diameter nodules of 85 (patient 11) to 150 mm (patient 15), respectively. Of the rest of the ten md cases, only one (patient 13 with surgically removed rectal paragaglioma, a non-representative carcinoid tumor) showed a stable disease. The other nine cases having an average of 3.3-mm diameter per nodule responded objectively (one complete plus eight partial, Fig. 6) in a cut-off value of ≈41 GBq (Fig. 7).

Based on the aforementioned analysis and observing Figs. 6 and 7, we arrive on the crucial point in which cases this treatment might be used. Neuroendocrine nodules of large volume of infiltrations spread into the hepatic parenchyma have shown poor response from the beginning of the treatment because the indium-111 Auger and conversion electron ranges are insufficient to kill large tumour cell populations and essentially inhibit the progressive tumour growth. Furthermore, the diffuse (non-measurable) disease has no hope for improvement. For this reason, radiotracers of longer range, addressed to larger number of tumour cells have been introduced with promising results as previously reported [34–37, 41]. Applied in combination (e.g. indium-111/luthetium-177) and exploiting the different element ranges, tagging cell targets of different distances from the locus of their uptake, they might increase the tumour-cell destroy capability.

Conclusion

In principal, three main illations characterise this non-random, clinically conducted investigation: (a) the effectiveness of the high doses of ^{111}In-DTPA-Phe-octreotide that is repeatedly administered after selective catheterization of the hepatic artery, (b) the type of emission—Auger and internal conversion electrons—that prohibits any nephrotoxicity, apart from some negligible side effects (temporal discomfort, rush, vomiting tension and rarely diarrhea), and (c) mainly the size—small to moderate—of the liver nodules and, secondary, their numbers that constitute the eligible criterion for proceeding with this kind of therapy. The results so far are promising for the local control of such a histotype of malignancies; on the other hand, the relatively satisfactory long (38 mo after the last therapy treatment) follow-up period of these patients allows room for a reliable estimation of the success rate according to response. The technique (catheterisation) highly optimises the received dose to the tumour, reducing consequently the burden of the critical organs. What remains is to evaluate, after a decade, the mortality rate of these patients as well as to investigate furthermore a possible combined use (cocktails) of isotopes with different ranges and energies so as to tag and destroy any tumour size.

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