

Natural ghrelin in advanced cancer patients with cachexia, a case series

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Abstract:

Background

Natural ghrelin, a peptide growth hormone secretagogue has a therapeutic potential in cachexia. We designed a dose-finding trial of subcutaneous natural ghrelin to improve nutritional intake (NI) in advanced cancer patients.

Methods

Advanced cancer patients with cachexia management (symptom management, physiotherapy, nutritional and psychosocial support) started with ghrelin at 32 µg/kg body weight, followed by 50% dose increases. Patients self-injected ghrelin twice daily for four days followed by a wash-out period. After reaching the primary endpoint, Maximal Nutritional Intake (MD-MANI), a maintenance period followed during which patients injected 10 doses of ghrelin per week. Safety parameters, NI, and cachexia outcomes (symptoms, narratives, muscle mass and strength) were measured over six weeks.

Results

10 patients with metastatic solid tumors were included and six (100% male, mean age 61.8 ± 8.5 SD) received ghrelin. MD-MANI was reached in four patients. Three patients reached the end-of study visit. Ghrelin was well tolerated with variable results on appetite and eating related symptoms but a positive effect in the narratives. Mean Functional Assessment of Appetite & Cachexia Therapy (FAACT) score was 6.8 points lower at final measurement compared to baseline, $t(5)=5.98$, $p<.01$). Muscle mass was stable in two patients and increased in one patient and muscle strength was stable in three patients. Subjective tolerability was high. Patients showed a fluctuating trajectory and median survival was 88 days (51-412 days).

Conclusion

Ghrelin was safe in advanced patients with cancer cachexia without dose-limiting toxicity and well tolerated. The intervention was very complex and the number of patients included small. There was a positive effect on nutritional intake and patient narratives.

Key Words: Ghrelin, Cancer Cachexia, Appetite, Muscle Mass

Background

Cancer cachexia remains a frequent problem in advanced cancer patients and their families.[1] It ranges from 24% of advanced cancer patients at the time of diagnosis to >80% at the terminal stages. [2] Cancer cachexia is clinically relevant because it is related to poor performance status, poor tolerance of anti-neoplastic treatments,[3] increased pulmonary infections, symptoms such as fatigue/asthenia,[4] anorexia, early satiety, chronic nausea, shortness of breath, sleep/wake disturbances, malaise, altered body image, family distress, [5] and ultimately, unnecessary suffering [6] and shorter survival.[7]

Key components of cachexia are integrated into clinical classification and assessment: 1) anorexia/reduced food intake, 2) catabolic drive (caused by inflammation and tumor activity), 3) decreased muscle mass and strength, 4) impact of cachexia (psychosocial, physical functioning).[8] Current treatments of cancer cachexia include both standard management and pharmacological and nutritional interventions. Standard palliative cancer care provides treatment of the so-called secondary reasons for cachexia and loss of appetite/decrease nutritional intake, such as stomatitis, dysphagia, uncontrolled symptoms, constipation etc.[9]

A basic nutritional counselling program should be in place to treat dietary problems and support conscious control of eating. Nutritional interventions for cancer-related cachexia, including enteral and parenteral nutrition and nutritional counselling, have limited effect on only a minority of patients and isolated positive outcomes. Physical activity counselling should encourage patients to make minimal physical stimuli to their muscles. Because emotional and social aspects can affect food intake, psycho-social support should be in place in order to relieve eating related distress of patients and family members. As pharmacological treatments, currently only progestin (effect on appetite, body weight, mainly water, thromboembolic complications), corticosteroids (short term effect of less than a few weeks, then insulin resistance, muscle wasting and increased risk for infections) and prokinetic agents (mainly for patients with early satiety) are available.[10]

Ghrelin, a 28 amino acid peptide discovered in 1999, is an endogenous ligand for the growth hormone secretagogue receptor, displaying dose-dependent growth hormone-releasing activity. [11] Ghrelin is predominantly secreted by gastric endocrine cells. When administered peripherally it stimulates growth hormone secretion, food intake, triggers a positive energy balance and produces weight gain through a central mechanism involving hypothalamic neuropeptides. Ghrelin increases during periods of fasting or under conditions associated

with negative energy balance such as starvation or anorexia. In contrast, ghrelin levels are low after eating, or with hyperglycaemia, and in obesity.

Ghrelin has had stimulatory effects on appetite and food intake, lean body mass, gastrointestinal motility, energy metabolism and it has alleviated cancer chemotherapy-associated dyspepsia.[4, 12, 13] Ghrelin has a possible effect on skeletal muscle mitochondrial function, inflammatory changes, and insulin signaling. [14]

In one pilot study, seven cancer patients had 31% higher energy intake with intravenous ghrelin than with placebo (5pmol/kg/min for 180 minutes) with no adverse effects. [13] A trial on intravenous ghrelin reports good tolerability and safety of single intravenous application of 2 and 8µg/kg ghrelin iv. [15]

The aim of this trial is to investigate the effect of individually dose-optimized (dose escalation) twice-daily subcutaneous (s.c) natural ghrelin on safety, toxicity, tolerability, nutritional intake, anorexia, eating-related symptoms, muscle mass and strength and physical function in advanced cancer patients.

METHODS

Patient population

Adult patients were recruited in the outpatient and inpatient services of the Oncology Department at the cantonal hospital St.Gallen, Switzerland, specifically from specialized cancer cachexia clinics.

Patients with any type of advanced incurable solid tumor and cancer cachexia were assessed for eligibility. The tumor situation had to be expected to remain stable without rapid progression in the next weeks. Anti-neoplastic treatment was allowed if it was given continuously, defined as weekly, or biweekly, and if the treatment did not cause more than grade 1 adverse event (AE) of decreased oral intake and gastrointestinal dysfunction.

Cancer cachexia was defined as the involuntary loss of weight of 2% of total body weight in two months or 5% in six months and was ongoing in recent weeks. Patients had to be able to eat, defined as no severe structural barriers in the upper gastrointestinal tract and no bowel obstruction. Patients were not allowed to have corticosteroids except for maximum of two days for chemotherapy, no progestin therapy within the last two weeks, and no anabolic drugs within the last month. Prokinetic medications were allowed, if given in a fixed dose for two weeks before study start and expected to be continued during the trial period.

Laboratory test results must have been within these ranges: Absolute neutrophil count $\geq 1.5 \times 10^9/L$, Platelet count $\geq 100 \times 10^9/L$, Serum creatinine ≤ 2.0 mg/dL, Total bilirubin ≤ 1.5 mg/dL, and AST (SGOT) and ALT (SGPT) $\leq 2 \times$ ULN or $\leq 5 \times$ ULN if hepatic metastases are present.

Presence of a normal level of consciousness with a mini mental status of $\geq 25/30$ points was required and the patient had to give informed consent.

Intervention

After basic cachexia management the study was divided into a titration period and a maintenance period.

Basic cachexia management

Patients were instructed about individual regular physical activity by a physical therapist and received basic psychosocial/spiritual assessment and treatment. Patients had at least one nutritional counselling session by a

specialized nutritionist for optimization of nutritional intake (multiple small meals, food preference, etc.) and for the instruction of recording nutritional intake.

Ghrelin was applied by the research staff at the clinic. During the maintenance period home-application was performed. Ghrelin applied at patients' homes was handed out as vials containing powdered ghrelin. The patient stored the vials for a maximum of one week in a special box in the freezer.

The starting dose was 32 µg/kg body weight, which has been shown to be safe in human beings. After the first three patients, the starting dose level was increased to Level 2. In the first 4 dose levels, the dose was increased by 50%. From the 5th dose level onwards the increase was 25%:

- Dose level 1 = 32 µg/kg
- Dose level 2 = 48 µg/kg
- Dose level 3 = 72 µg/kg
- Dose level 4 = 108 µg/kg
- Dose level 5 = 135 µg/kg
- Dose level 6 = 169 µg/kg
- Dose level 7 = 211 µg/kg

The maximum tolerable dose was set as 20 mg ghrelin (equivalent to 5ml) due to the high drug volume to be administered subcutaneously (s.c.). Volumes of > 2.5ml had to be divided into two syringes, i.e. the subject had to be injected twice. The first dose of each dose level was always administered in the clinic for safety reasons.

Titration period in hospital

During the titration period treatment was conducted with twice daily s.c. ghrelin injection for two days.

Maintenance period in hospital and at home.

All patients who reached the maintenance period injected ghrelin twice daily on 21 days (on five out of seven days per week, i.e. Monday to Friday)

Outcomes

Nutritional intake

Nutritional intake was measured according to best practice adapted to the individual patient. This was done using a food diary, photographs, and the use of a digital scale to weigh meals. In addition, the nutritionist called the

patients once per day to remind him/her to complete the food diary. The nutritionists estimated the caloric equivalent of food eaten.

Definition of Minimal Dose for Maximal Nutritional Intake (MD-MANI)

For each individual patient, data was reviewed to establish the lowest ghrelin drug level associated with the maximum caloric nutritional intake in a 24-hour period (MD-MANI). A substantial increase in intake was defined as at least 10% more caloric intake compared to the baseline. Doses were escalated as long as a substantial increase in intake was measured and no toxicity occurred. MD-MANI was determined when no significant increase was measured anymore or toxicity occurred. At this point patients were referred to the maintenance period.

Toxicity and tolerability

The maximal ghrelin dose level was deemed to be one at which there was no grade 3/4 adverse event (AE) or serious adverse event (SAE) likely associated with the investigational product. Common toxicity criteria (CTC) from the time of first drug administration until study termination and 30 days follow-up were applied. The assessment of any grade AE and SAE included neuropsychologic side effects (like e.g. dizziness) and injection site reactions and haematological/ biochemical alterations. Assessments were done according to good clinical practice (GCP).

Anorexia Eating-related Symptoms, Narratives

Anorexia assessment was performed using the Edmonton Symptom Assessment Scale (ESAS). [16] Eating related symptoms like appetite, satiety, nausea, abdominal discomfort and dyspepsia were assessed by the modified German Functional Assessment of Appetite & Cachexia Therapy (FAACT⁺), which includes 15 items in a 4-point categorical scale. FAACT⁺ is an adapted and translated version of the FAACT questionnaire.[17] Additionally, narratives from patients and proxies were collected.

Muscle mass and Muscle strength (muscularity)

Muscle mass was measured by abdominal CT scan. Images were analysed using Slice-O-matic software V4.3 (Tomovision) using pre-established thresholds of Hounsfield unit.[18, 19]

At each time point, Hand Grip strength was measured six times. Compliance of the patient was estimated in order to get reliable test results. The mean value out of all six measures of each hand was calculated. (JAMAR® Hand Dynamometer) [20]

Physical function

A validated activity monitor the ActivPAL (PALTechnologies Ltd, Glasgow, Scotland), based on a uni-axial accelerometer was used. [21] It identifies episodes of walking, sitting and standing, allowing the measurement of

both activity and inactivity, Furthermore it records the number of steps and instantaneous cadence. Each time span of measurement was three days.

Statistical analyses

All patients were included in the analyses. Descriptive analysis was performed. Paired t-tests were conducted on pre-post ghrelin measurements. The level of statistical significance was set at $p < .05$.

Ethical considerations

The study protocol was written and the trial was performed in accordance with the Declaration of Helsinki, the Guidelines of Good Clinical Practice issued by ICH and Swiss regulatory authority's requirements.

The Study was approved by the local ethics committee (EKSG SG 294/08).

RESULTS

Over a one-year period, patients in the cachexia clinics were screened for trial participation. The CONSORT-diagram is displayed in Figure 1.

10 patients were included in the study, but only six patients received the investigational product. The remaining 4 patient never got the drug due to rapid progression of the cancer disease.

Age ranged from 48 years to 76. The tumor types represented were pancreatic, head & neck, lung and gastrointestinal cancer. Average weight loss in the last six months was 15 kg.

An overview on patient demographics is given in Table 1 and MD-MANI is presented in Table 2. In the following paragraphs, patients receiving Ghrelin are described case by case:

Patient 1

A 61-year-old male with pancreatic cancer, which had metastasized to the liver, presented with a weight of 75 kg and Body Mass Index (BMI) of 25.4. In the previous six months, he had lost 17 kg, 15 kg of which had been lost in the previous two months. He received Gemcitabine. He had a Karnofsky score of 80 and an Eastern Cooperative Oncology Group (ECOG) score of 1. This patient reached MD-MANI at Dose Level 2 with a 14% increase in kcal intake compared to baseline. Patient 1 commented about his experience using ghrelin saying, *“I don't leave home without a snack”* and *“I have to eat every two to three hours.”* Comparing pre-study measurements to post-study measurements, he exhibited no change in muscle mass, a 2% increase in muscle strength, a 7% decrease in steps/day. This patient survived 412 days.

Patient 2

A 66-year-old male with pancreatic cancer, which had metastasized to the lymph nodes, presented with a weight of 52 kg and a BMI of 17.9. He had lost nine kg in the previous six months, including 0.4 kg of weight gain in the previous two months. He received Gemcitabine. He had a Karnofsky score of 70 and an ECOG core of 2. MD-MANI could not be established for this patient. At all ghrelin dose levels, kcal intake was lower than baseline, with the exception of Dose Level 2, when there was a 2% increase in kcal intake. This small increase did not meet the pre-set definition of MD-MANI being at least 10% increase in kcal compared to baseline. Patient 2 experienced a SAE, an episode of hypothermia, which was deemed attributable to the ghrelin application. Nonetheless, this patient reported positive impressions of taking ghrelin, stating, *“I feel fresher and I eat more.”* Over the course of the study, he exhibited a 5% decrease in muscle mass. Post-study measurements of muscle strength, steps/day were not available. This patient survived 53 days.

Patient 3

A 76-year-old male with gastrointestinal cancer, which had metastasized to the liver, presented with a weight of 48 kg and a BMI of 16.0. In the previous six months, he had lost 14 kg, 13 of which had been lost in the previous two months. He received Capecitabine. He had a Karnofsky score of 60 and an ECOG score of 2. This patient reached MD-MANI at Dose Level 4, when there was an 18% increase in kcal intake compared to baseline. Patient 3 made the following comment about using ghrelin: *“Feel more active.”* During the study period, Patient

3 was hospitalized for atrial fibrillation, which was a SAE deemed unrelated to ghrelin. This patient survived 51 days.

Patient 5

A 63-year-old male with advanced mesothelioma presented with a weight of 70 kg and a BMI of 22.6. Data regarding weight loss in the previous six months was not available.. He received FOLFIRI. He had a Karnofsky score of 60 and an ECOG score of 1. This patient reached MD-MANI at Dose Level 3 with a 29% increase in kcal intake compared to baseline. Patient 5's opinion about using ghrelin was positive, saying, "*This is the first therapy which improves my well-being.*" Patient 5 experienced an increase in tumor pain, a SAE deemed unrelated to ghrelin. Comparing pre-study measurements to post-study measurement, he exhibited a 3% decrease in muscle mass. Post-study measurements for muscle strength, steps/day could not be obtained. This patient survived 62 days.

Patient 9

A 48-year-old male with head & neck cancer, which had metastasized to the lungs, liver and lymph nodes, presented with weight of 35 kg and a BMI of 15.8. He had lost 17 kg in the previous six months, of which 11 kg had occurred in the previous two months. He did not receive chemotherapy. He had a Karnofsky score of 80 and an ECOG score of 1. This patient reached MD-MANI at Dose Level 3, at which point the patient took in 11% more kcal compared to baseline. A secondary malignancy was diagnosed in Patient 9, a SAE deemed unrelated to ghrelin. Comparing pre-study measurements to post-study measurements, he exhibited a 9% decrease in muscle mass, a 6% increase in muscle strength, a 19% decrease in steps/day. This patient survived 114 days.

Patient 10

A 57-year-old male with head & neck cancer, which had metastasized to the lungs, presented with a weight of 59 kg and a BMI of 18.6. He had lost 19 kg in the previous six months, including three kg of weight gain in the previous two months. He received Cetuximab. He had a Karnofsky score of 90 and an ECOG score of 1. This patient reached MD-MANI at Dose Level 3 when kcal intake increased 11% compared to baseline. Patient 10 commented that on ghrelin, "*my stomach growls*". Comparing pre-study measurements to post-study measurements, he exhibited no change in muscle mass, a 6% increase in muscle strength, a 16% increase in steps/day. This patient survived 166 days.

Anorexia and eating related symptoms

Anorexia, as measured on a visual analogue scale (VAS), showed fluctuation during the study as shown in **Figure 2**. FAACT Sum scores trajectories are displayed in **Table 3**. A paired t-test showed that mean FAACT scores were 6.8 points lower, significantly lower at the final measurement as compared to the first measurement,

$t(5)=4.88$, $p=0.005$. A paired t-test of first and last VAS measurements showed no statistically significant change, $t(5)=-0.47$, $p=0.67$.

Muscle mass and strength, physical activity

Muscle mass was stable in two patients and increased in one patient and muscle strength was stable in three patients. The full results can be seen in Table 4.

The change in steps walked was also highly variable, depending on the patient. The change in step count from first measurement to last measurement ranged from -92% to 100%. The difficulties of measuring physical activity among a palliative cohort were apparent. For example, Patient 5 was non-compliant when it came to using the ActivPAL device, due to his perception that the device was inconvenient. Results are displayed in Table 5.

The injections were well tolerated at the injection site and subjective tolerability was high. Patients showed a fluctuation trajectory and survival was short: median survival was 88 days (min 51 days; max 412 days).

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DISCUSSION

All six patients who received s.c. ghrelin in the study suffered from far advanced cancer and experienced major weight loss. Five of the six patients were under anticancer treatment. All of them were male. Ghrelin was well tolerated and was perceived positively by individual study participants. There was a positive effect on nutritional intake and MD- MANI could be determined in four out of six patients. There seemed to be an effect with titration but without linearity. Overall, a definite dose for maximal nutritional intake could not be decided due to the variability of patient outcomes and the small sample size.

The two best responders went into a compassionate use program because they did not want to abstain from the drug. This was approved by the ethics committee. There was a change in appetite, and according to patient narratives, eating experience and eating-related symptoms also improved.

During the trial four serious adverse events occurred. A clinical relevant hypothermia was considered to be related to the investigational product.[22] The other events were considered as not drug related. An occurrence of a secondary malignancy was seen; this was considered as not unusual in a patient heavily pretreated with several cytotoxic agents.

Muscle mass and muscle strength measures yielded variable results and AcitvPal measurement encountered technical challenges with extreme fluctuations in activity between days. More measurements and longer measurement times could have improved the chances of drawing meaningful conclusions. A positive effect on muscle mass is difficult to measure in an advanced cancer population because the natural course of muscle loss is difficult to predict. Additionally, symptoms perception and subjective narrative response is influenced by several factors, such as motivation, stimulation by proxies and rapport with the treatment team.

In recent years, several trials have been conducted with substances similar to ghrelin. Anamorelin, a synthetic growth hormone secretagogue receptor agonist, has been investigated in chemotherapy trials to increase lean body mass and improve muscle strength. Anamorelin improved muscle mass but not the functional co-primary functional outcome, handgrip strength.[23, 24] FDA and EMEA declined approval, but ghrelin and analogue substances remain an interesting topic in cachexia research.

The strength of the present case series is the innovative design and the measurement of state-of-the-art outcomes in cachexia research. A major weakness is the low number of patients included. Conducting the study was very laborious, and it was challenging to find stable phases in dynamic trajectories near end of life. Because there was no comparator, the study is prone to placebo effects.

Patients with advanced cancer experienced unexpected tumor progression and presented with heavily fluctuating symptoms, which affected nutritional intake. To reflect the proposed effect of ghrelin on appetite, food intake, muscle, inflammation and psychological measurements, a multitude of outcomes representing different domains of cancer cachexia were measured, because meaningful outcomes in cancer cachexia research remain a matter of debate.[25] These target outcomes may change along the trajectory of cancer cachexia.[26] In the early stage of cachexia, muscle mass and function are the central focus. An effective drug could even prevent the development or progression of cachexia. This is in contrast to the end stage of cachexia, when symptom control and palliation become priorities. In this series, Ghrelin was applied mainly near the end of life, but further study of Ghrelin is

compelling because it is one of the few substances that could potentially have a positive effect along the whole cachexia trajectory.

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The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle[27..]

Conflict of Interest:

David Blum, Susanne de Wolf-Linder, Rolf Oberholzer, Michael Brändle, Thomas Hundsberger and Florian Strasser declare that they have no conflict of interest.

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Figure1: CONSORT Flow Diagram

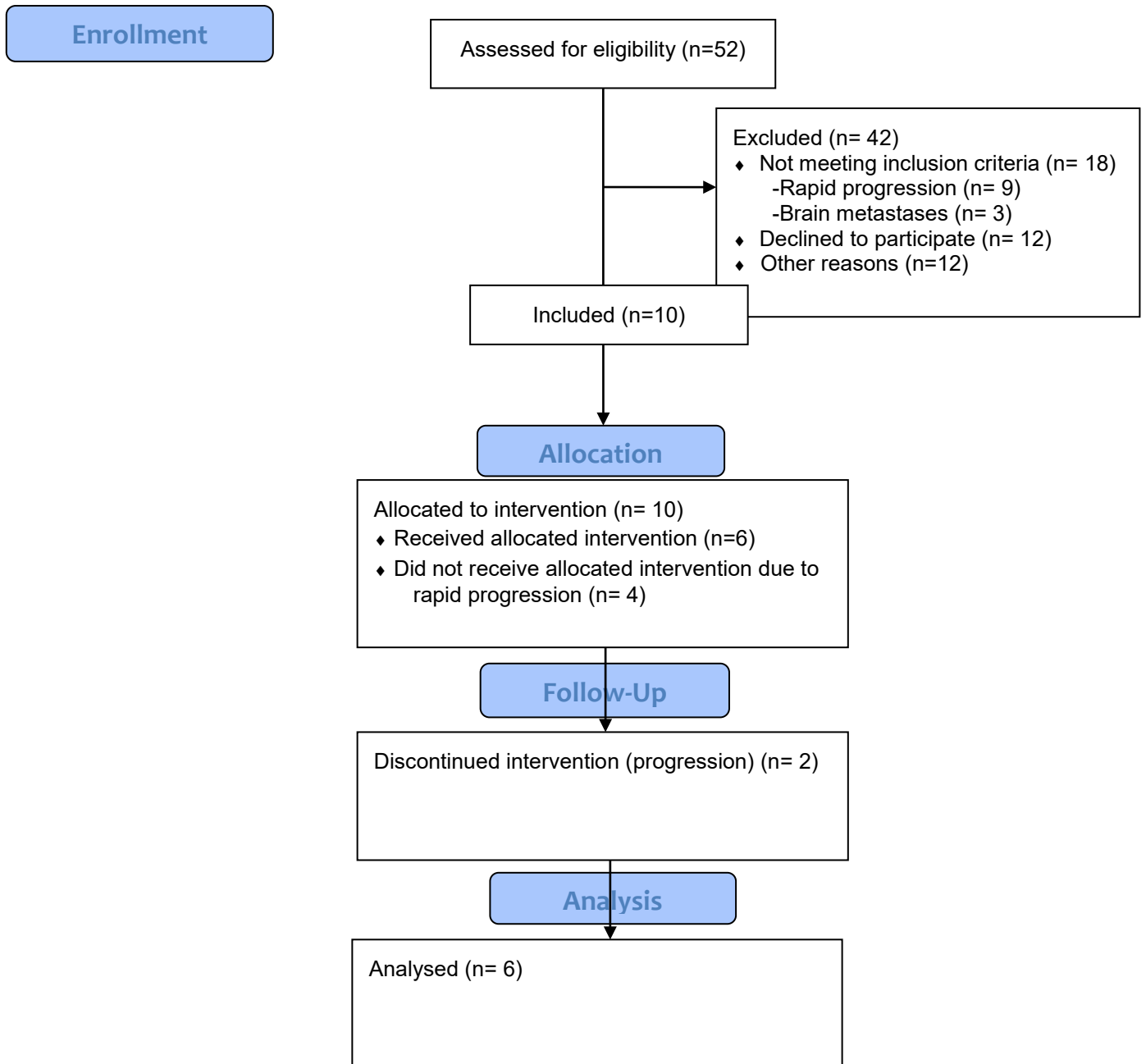
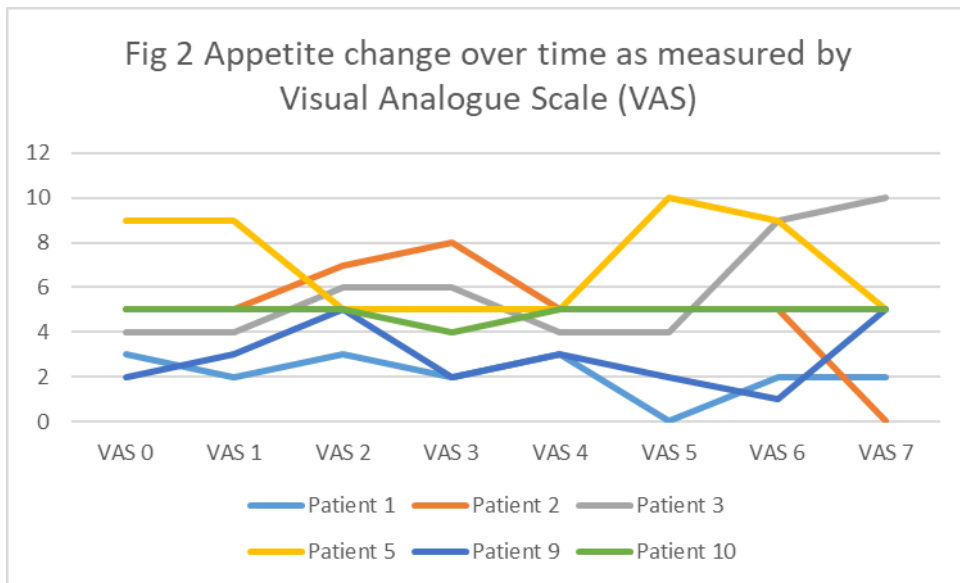


Figure2: Appetite



Appetite VAS (1-10, 0 best, 10 worst)

Patient	Tumortype:	Metastasis¹	Chemotherapy	age (years)	sex:	Karnofsky	ECOG	Weight (kg)	BMI (kg/m2)	WI2m (kg)	WI6m (kg)	NI%	Trajectory	Survival
1	Pancreas	2, 5	Gemcitabine	61	m	80	1	75	25,4	-14,7	-16,7	75	PR	412d
2	Pancreas	4,5	Gemcitabine	66	m	70	2	51,6	17,9	0,4	-9,2	15	N/A	53d
3	Gastrointestinal	2,5	Capecitabine	76	m	60	2	48	16,0	-12,5	-14,3	15	N/A	51d
5	Mesothelioma	6	Capecitabine Irinotecan	63	m	60	1	70	22,6	1-1,4	N/A	30	PD	62d
9	Head & Neck	1,2,4, 5	None	48	m	80	1	35	15,8	-11,4	-16,7	73	PR	114d
10	Head & Neck	1,6	Cetuximab	57	m	90	1	59	18,6	3,4	-19,2	85	PD	166d

Metastasis location, 1=lung; 2=liver; 3=brain; 4=lymph node; 5=other; 6=none; WI2m: weight loss two months; WI6m: weight loss six months; NI%: Nutritional Intake; d: days

Tab 2: Nutritional Intake with MD MANI in bold								
Patient 1	Dose Level	1	2	3	4	2	2	2
	Kcal	2350	2691	2415	2627	2650 kcal	2005	2581
	Increase BL	0 %	+ 14%	+3 %	+12%	+12 %	- 15%	-10 %
Patient2	Dose Level	1	2	3	4	5	0	0
	Kcal	934	1394	1345	999	752	971	1047
	Increase BL	-31,50%	2 %	-1 %	-26.8%	-44 %	- 28%	-23%
Patient3	Dose Level	1	2	3	4	5	4	0
	Kcal	1061	1189	1285	1331	1275	337	246
	Increase BL	-6 %	+6%	+14%	+18 %	+13%	-70 %	-78 %
Patient 5	Dose Level	2	3	4*	5	3	3	3
	Kcal	1580	1908	1585	1553	1220	1554	1843
	Increase BL	+7%	+29%	+7%	+5%	-18%	+5%	+25%
Patient9	Dose Level	2	3	4	5	3	3	3
	Kcal	3035	3544	3044	3194	3404	3125	2559
	Increase BL	-5%	+11%	-5%	-0%	+6%	-35	-20 %
Patient10	Dose Level	2	3	4	3	3	3	
	Kcal	1900	2029	2027	1913	1863	2322	
	Increase BL	+3 %	+11 %	+10%	+4 %	+1 %	+26 %	

• Due to S-NIS trial chair decided to rise one level

MD-MANI: Minimal Dose for Maximal Nutritional Intake; BL base line,

Tab 3 FAACT (Functional Assessment of Appetite & Cachexia Therapy)								
	FAACT 0	FAACT 1	FAACT 2	FAACT3	FAACT 4	FAACT 5	FAACT 6	FAACT 7
Patient 1	33	31	31	32	33	33	30	30
Patient 2	38	28	27	27	31	33	N/A	N/A
Patient 3	34	30	33	27	24	26	N/A	N/A
Patient 5	35	35	34	33	34	35	35	22
Patient 9	38	41	41	37	40	37	40	32
Patient 10	38	33	31	30	31	35	32	N/A

FAACT (lower scores better)

Table 4	Muscle Mass and strength					
	Muscle Mass TAG cm ³			Muscle Strength: kg		
	Before	After	% change	Before	After	% change
Patient 1	115	115	0%	28,4	28,9	2%
Patient 2	95	90	-5%	17,8	ND	N/A
Patient 5	155	150	-3%	12,0	ND	N/A
Patient 8	115	125	9%	44,6	43,7	-2%
Patient 9	120	109	-9%	35,0	37	6%
Patient 10	115	115	0%	34,0	36	6%

Table 5: Daily Step Counts

Patient Number	Date	Daily Step Count	% Change
1	23/06/09	2210	
1	24/06/09	2828	
1	25/06/09	4418	
1	13/07/09	4796	
1	14/07/09	5596	
1	15/07/09	4956	
1	01/08/09	5616	
1	02/08/09	3294	
1	03/08/09	3938	
1	11/12/09	6948	
1	12/12/09	1806	
1	13/12/09	1896	
1	14/12/09	2056	-7%
2	23/06/09	2210	
2	24/06/09	2828	
2	25/06/09	4418	100%
3	10/08/09	6764	
3	01/09/09	532	-92%
5	-	-	-
9	25/03/10	2886	
9	26/03/10	3852	
9	27/03/10	5884	
9	28/03/10	3836	
9	29/03/10	1302	
9	16/04/10	6662	
9	17/04/10	10812	
9	18/04/10	3936	
9	19/04/10	202	
9	07/05/09	3234	
9	08/05/09	6940	
9	09/05/09	2342	-19%
10	20/07/10	5400	
10	21/07/10	6748	
10	22/07/10	3228	
10	23/07/10	3650	
10	24/07/10	2340	
10	27/08/10	7718	
10	28/08/10	6896	
10	29/08/10	2740	
10	30/08/10	13622	
10	31/08/10	860	
10	01/09/10	6290	16%