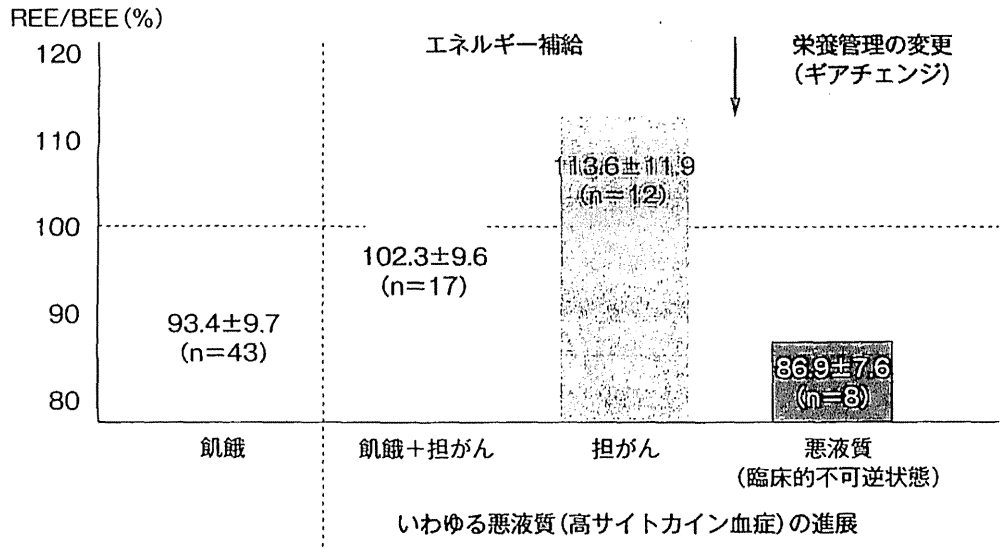

図1　エネルギー消費量とがんの進展(文献2より引用)
REE/BEE：1日あたりの安静時エネルギー消費量(間接熱量計による)/基礎代謝エネルギー消費量(Harris-Benedictの式による)

告され，腫瘍進展度，栄養状態，罹病期間などとの関係性は認めなかったと報告されている．一方，当講座の感染徴候がない担がん患者に対する臨床研究では，適切な栄養管理が行われている場合は，エネルギー消費量が高値であった．しかし，最終的に生体は不可逆的な代謝動態に陥り，その結果，エネルギー消費が逆に抑制されることが明らかになってきた(**図1**)[2]．また，がんの原発部位によりREEの亢進は異なり，胃がん，大腸がん，直腸がんなどでは予測値と変わらないが，膵がん，肺がんなどでは亢進するとの報告もあり，今後のさらなる詳細な研究が期待される[3,4]．

糖代謝異常

担がん状態での糖代謝異常として，①腫瘍細胞のグルコース消費亢進によるグルコース代謝回転の増大，②Cori回路の活性亢進，③アミノ酸からの糖新生の亢進，④インスリン感受性の低下などが挙げられる．すなわち，担がん状態においては，腫瘍そのものの糖消費増大により，がん組織が嫌気性解糖系を中心にグルコースをエネルギー源として消費し，乳酸を産生する結果，肝でのCori回路の活性亢進を招き，乳酸からの糖新生が亢進することとなる．Cori回路の異常な活性化が，低栄養のがん患者に認められており，この亢進した活性は，約300 kcal/日の喪失に相当すると言われている[3]．アミノ酸からの糖新生について，がん悪液質患者では，血清アラニン，グリシン，グルタミン濃度が低下していることがある．これは，肝において糖新生のためにこれらのアミノ酸の利用が亢進していることに関係していると考えられている．

蛋白代謝異常

担がん状態での蛋白代謝異常として，①骨格筋蛋白の分解亢進，②骨格筋蛋白の合成低下，③がん細胞における蛋白合成の増加，④全身での蛋白代謝亢進，⑤肝での蛋白合成亢進などが挙げられる．すなわち，担がん患者における全身の蛋白・アミノ酸の代謝亢進は，骨格筋蛋白

の分解亢進，合成低下(異化)に伴って，肝における蛋白合成亢進により引き起こされる．このため，がん患者の多くが負の窒素バランスとなるとともに，急激な除脂肪体重(lean body mass：LBM)の減少を誘発し，sarcopeniaに陥ってしまう．さらに最近では，がん細胞自身から放出される蛋白分解誘導因子(proteolysis-inducing factor：PIF)が，骨格筋の蛋白異化を起こす主要な経路であるアデノシン三リン酸(ATP)-ユビキチン依存経路の活性化に関与していることも明らかになってきた[3]．

脂質代謝異常

担がん状態での脂質代謝異常として，①脂質分解の亢進，②脂質合成の低下，③全身の脂肪量の低下，④lipoprotein lipase(LPL)の活性低下，⑤血中トリグリセライドの上昇などが挙げられる[5]．すなわち，がん悪液質患者の多くは，相当量の脂肪組織が喪失する．この喪失は，脂肪合成の低下よりも分解の亢進によるものが大半である．脂肪分解亢進には，摂食不良，インスリン抵抗性，がん細胞自身から放出される脂肪動員因子(lipid mobilizing factor：LMF)などが関与している[3]．さらに，LPLの活性低下，脂質合成の低下は，tumor necrosis factor(TNF)，interleuikin(IL)-1，interferon(IFN)-γなどのサイトカインが関与していると考えられている．また，がん患者に認められる高トリグリセライド血症は，LPLの活性低下，あるいは脂肪合成に影響を及ぼすサイトカインが関与している[5]．

がん患者が陥る悪液質

がん患者が陥る悪液質の特徴は，脂肪組織のみならず骨格筋の多大な喪失(骨格筋の喪失：sarcopeniaあるいはmyopenia)を呈することで，脂肪組織の減少が主であり，骨格筋の大きな喪失を伴わない単なる飢餓状態とは対照的である．一般的な栄養管理を行っても悪液質を改善できないことから，サイトカインや腫瘍由来物質の産生が要因として存在することが1990年代後半から注目されるようになった．すなわち，がん悪液質は単なる栄養学的異常ではなく，代謝，免疫学的異常などによって引き起こされる病態と考えられている．

悪液質の病期

欧州静脈経腸栄養学会(ESPEN)において，悪液質の状態を，pre-cachexia → cachexia → refractory cachexiaに分類する3段階の病期(stage)が提唱された．すなわち，代謝異常が軽度で，明らかな悪液質の症状を呈さない，悪液質(＝cachexia)の前段階の状態は，“pre-cachexia”と呼ばれ[6]，一方，高度代謝障害により，栄養サポートを行っても栄養状態の改善余地がない最終末期の悪液質状態は，“refractory cachexia”とされている(**図2**)[7]．現在では，悪液質の進展が少ない，すなわち代謝異常の程度が軽度である段階で，適切な栄養サポートを行うことが重要であり[7,8]，この早期からの栄養サポートによって，栄養不良の進展を遅らせたり，ほかの原因による栄養不良を改善させ，抗がん治療への耐用性を向上できるものと考えられるようになった[8]．

悪液質の病期を考慮した代謝・栄養管理：輸液・栄養管理実施基準

再発がん患者であっても，前述したrefractory cachexiaに陥っていないがん患者に対する代謝・栄養管理は，悪液質に有効とされる栄養剤の投与を考慮するが，基本的には一般の患者に対する栄養管理とほぼ同様である．しかし，

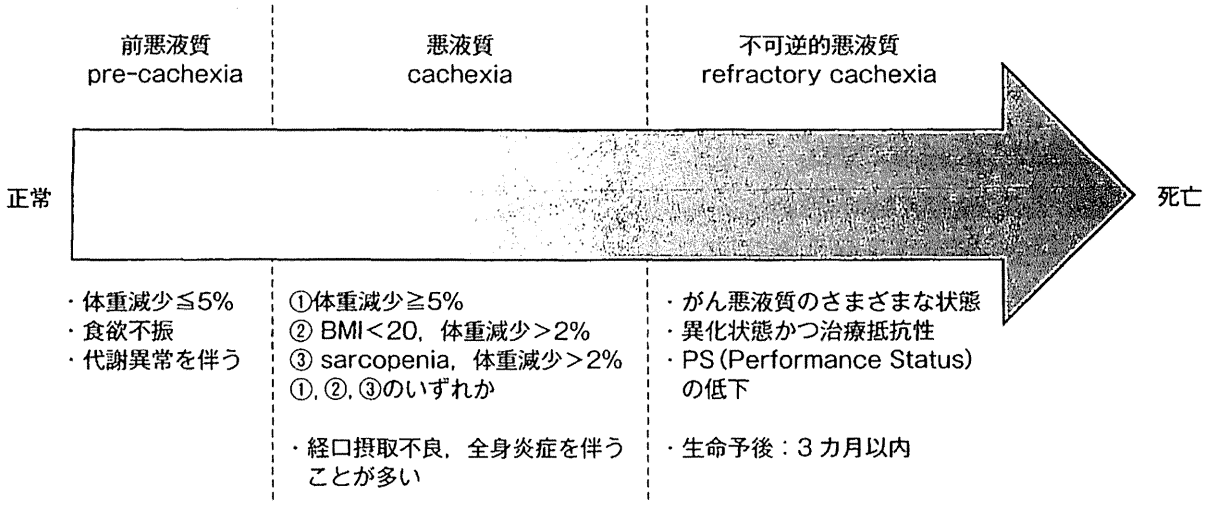

図2 悪液質の段階（文献7より引用，改変）
BMI：Body Mass Index

当講座で行った臨床研究では，前述のごとく肺炎などの感染徴候がなければ，残された余命が約2週間の時点で，生体は不可逆的な代謝動態に陥り，その結果，エネルギー消費が逆に抑制されることが明らかになってきた（**図1**）[2]．したがって，この時点が輸液・栄養管理の負荷軽減時期にふさわしいと考えられる．そこで，当講座では，refractory cachexiaに陥っているか，否かによって変更する「担がん・終末期がん患者に対する輸液・栄養管理実施基準」を設定し，実践している[9,10]．原則としてrefractory cachexiaに陥っていない症例の栄養管理は，過不足のないエネルギーや悪液質に有効な各種栄養素の投与を行う．refractory cachexiaが臨床的に明確になった場合には，負荷軽減することによって，過剰な水分やエネルギーなどの投与を抑制し，残されたわずかな身体機能に対する負荷を制御する（**表1**）．この実施基準に従って，輸液・栄養管理を実施したところ，がん終末期のさまざまな症状に対しても比較的コンプライアンスを高く維持可能であり，QOLの高い状況で最期を迎える患者が増加してきている．

表1 担がん患者の輸液・栄養管理（不可逆的悪液質）（文献9より引用）

A. 経口摂取可能症例
1. 自由摂取：好きな食事・食べられる食品（緩和ケア食など）
2. 本人の理解・承認が得られる場合：
   ①ビタミン・微量元素栄養剤
   ②高脂肪高蛋白栄養剤（肺転移・呼吸障害合併例）
   ③GFO（摂食不良症例，免疫能低下例，麻薬投与例）
   ④分岐鎖アミノ酸製剤（筋萎縮・四肢だるさ発症例）
   GFO：グルタミン・水溶性ファイバー・オリゴ糖

B. 経口摂取不能例
1. 本人・家族の希望：
   ①強制的な輸液
   ②間歇的輸液（末梢静脈栄養；ヘパリン/生食水ロック）
   ③持続的輸液（末梢静脈栄養/中心静脈栄養；長期ルート保持困難例）
2. 水分投与量：15~25 mL/kg体重/日（およそkg体重あたり20 mL/日；500~1,000 mL/日）
   注：口渇対策；輸液に頼らず口腔ケアをかねて緑茶スプレー（カテキン効果）を実施
3. 必要カロリー（kcal/日）：5~15 kcal/kg体重/日（およそ200~600 kcal/日）
4. 投与栄養素：
   ①糖質が中心
   ②必要に応じてアミノ酸（分岐鎖アミノ酸）・必須脂肪酸を少量投与
5. ビタミン・微量栄養素：一日必要量（口内炎，褥瘡発生予防のため）

不可逆的悪液質：高度がん進展による全身衰弱，コントロール不能な胸水・腹水，全身の浮腫合併例

まとめ

がん患者に対する治療は，がん縮小に対する効果，生存期間の延長だけではなく，患者のより高いQOLの維持によって評価されるべきである．すなわち，がん治療により少しの生存期間の延長が得られたとしても，食欲不振，嘔吐などのさまざまな副作用やactivity of daily living(ADL)低下に苛まれ，QOLが維持できなければ真の価値がないと考える．サルコペニアの進行を少しでも抑制し，QOLを最期まで維持し続けるための一手段として，適切な栄養管理を行うことはきわめて重要である．

文献

1) Demsey DT, et al : Energy expenditure in malnourished gastrointestinal cancer patients. Cancer 53 : 1265-1273, 1984
2) 東口髙志：がん悪液質の代謝動態からみた栄養管理．臨床栄養 113 : 602-607, 2008
3) Tisdale MJ : Cachexia in cancer patients. Nat Rev Cancer 2 : 862-871, 2002
4) Guirao X : Impact of the inflammatory reaction on intermediary metabolism and nutrition status. Nutrition 18 : 949-952, 2002
5) Argiles JM, Lopez-Soriano FJ : New mediators in cancer cachexia. Nestle Nutr Workshop Ser Clin Perform Programme 4 : 147-162, 2000
6) Muscaritoli M, et al : Consensus definition of sarcopenia, cachexia and pre-cachexia : Joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clin Nutr 29 : 154-159, 2010
7) Fearon K, et al : Definition and classification of cancer cachexia : an international consensus. Lancet Oncol 12 : 489-495, 2011
8) 東口髙志：輸液による栄養療法の基本．日本緩和医療学会緩和医療ガイドライン委員会(編)：終末期がん患者の輸液療法に関するガイドライン2013年版，pp26-33，金原出版，2013
9) 東口髙志，他：癌緩和医療における輸液・栄養管理．コンセンサス癌治療 7 : 162-165, 2008
10) 東口髙志：消化器がんの緩和ケア．菅野健太郎，他(編)：消化器疾患最新の治療 2011-2012，pp67-70，南江堂，2011

HOME PARENTERAL NUTRITION

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Michael Staun

and

André Van Gossum

7 Home Parenteral Nutrition in Japan

AKIHIRO ITO[1]*, TAKASHI HIGASHIGUCHI[2] AND HARUMASA OYANAGI[3]

[1]*Department of Surgery & Palliative Medicine, School of Medicine, Fujita Health University, Toyoake, Japan;* [2]*Chairman of Japanese Society for Parenteral and Enteral Nutrition, Department of Surgery & Palliative Medicine, School of Medicine, Fujita Health University, Toyoake, Japan;* [3]*Former Chairman of Japanese Society for Parenteral and Enteral Nutrition*

Introduction

To reform the medical system and improve quality of life (QoL) in Japan, home healthcare has recently been established as a third form of medical care, alongside in-patient care and out-patient care. Home parenteral nutrition (HPN) is a method of providing nutrition parenterally at home, to free patients from the hospital setting and allow them to return to their homes, lead a more normal daily life and resume their roles in society. When HPN is used in home healthcare, HPN is highly dependent on medical technology. In other words, HPN utilizes equipment and instruments ordinarily used in a hospital.

Parenteral nutrition is the only treatment by which patients with severe small bowel dysfunction such as short bowel syndrome (SBS) can receive adequate nutrition. HPN has been covered by medical insurance in Japan since 1985 and is now in wide use. HPN can safely be implemented if properly managed by patients and their families based on guidance from medical staff. This chapter presents an overview of HPN in Japan, including its indications, medical insurance coverage and increasing use.

Indications for HPN

HPN is generally indicated for diseases, regardless of medical insurance coverage, in which nutrition support is difficult to maintain other than by total parenteral nutrition (TPN) and for which a medical doctor judges that HPN is necessary. HPN is generally contraindicated in patients with chronically impaired oral intake

*E-mail: itoh@mctv.ne.jp

due to cerebrovascular disease, however, in whom digestion and absorption is not otherwise impaired. The indicated diseases can be broadly divided into two categories:

1. Benign diseases requiring long-term TPN. When the patient's condition is stable and life at home is not medically inconvenient.
2. Incurable end-stage malignancies when life at home would improve QoL. End-stage patients in Japan can spend time at home when their condition is stable, but a deterioration in general condition may require transfer to a medical facility such as a palliative care unit or provision of further caregiving at home.

Criteria for HPN

Guidelines (Shirotani, 2006) for parenteral and enteral nutrition by the Japanese Society for Parenteral and Enteral Nutrition (JSPEN) specify criteria for using HPN in adults and children. HPN is implemented based on these guidelines in Japan.

Criteria in adults

HPN is implemented based on these guidelines in adults as follows:

1. Home nutritional therapy should be implemented with the informed consent of not only the patients themselves, but also their caregivers (including family).
2. It is important that patients themselves or their caregivers are able to reliably implement the procedures for HPN.
3. If home nutritional therapy is necessary, enteral nutrition is preferable. In patients with digestive dysfunction in whom enteral nutrition cannot be adequately managed, parenteral nutrition is indicated.
4. Nutritional therapy should be monitored regularly.

Criteria in children

HPN is implemented based on these guidelines in children as follows:

1. If continued nutritional therapy is required in children whose disease is stable, HPN is indicated even for children.
2. HPN in children should be implemented in a suitable environment by caregivers or specialty medical staff who can provide nutritional management at home nearly equivalent to that in a hospital.
3. For HPN in children, caregiver education should begin before hospital discharge, and education and guidance should be continued even after the child is sent home.
4. For HPN in children, monitoring and nutritional assessment should be performed regularly, with particular attention on growth and development.

5. For HPN in children, a tunnelled silicone rubber catheter (Broviac catheter) is associated with fewer complications than a totally implantable port.

Prerequisites for implementation

The guidelines for HPN (Onodera, 2001) in Japan also recommend the following as prerequisites for implementation:

1. A decision should be made that in-patient treatment for the underlying disease is not necessary, that the condition is stable and that HPN will improve QoL.
2. The ability of medical staff to provide guidance on HPN must be sufficient and a system for managing HPN both within and outside the hospital must be established.
3. Both the patient and family should thoroughly understand the principles of TPN and the need for HPN, and both should then request HPN. A decision should be made that: (i) HPN can be implemented at home without problems adjusting intravenous fluids; (ii) infusions can safely be managed; and (iii) the risk of complications is low.

Contraindications for HPN

HPN is not indicated in patients with chronically impaired oral intake due to cerebrovascular disease, but in whom gastrointestinal function is otherwise normal, including:

- patients with senile dementia;
- patients with sequelae of stroke, intracerebral haemorrhage or post-traumatic head injury;
- patients in a vegetative state; and
- patients with amyotrophic lateral sclerosis, muscular dystrophy or Parkinson's disease.

TPN is generally contraindicated in patients with these diseases and conditions. Instead, enteral nutrition is indicated. HPN is also contraindicated:

- when a disease is unstable.

With fever due to intraperitoneal abscesses, gastrointestinal fistulas, urinary tract infections, respiratory tract infections or unknown cause, it is safer not to transfer patients to HPN. In addition, HPN should not be implemented when insulin control is unstable, such as in severe diabetes.

Treatment Reimbursement in Japan

As of 2008, reimbursement from the Social Insurance/Elderly Health Insurance systems is calculated as follows.

For HPN

Among patients with extensive intestinal resection or bowel dysfunction due to various causes, HPN is a method of nutrition implemented by patients themselves at home after discharge from a hospital in stable condition. These patients, regardless of the causative disease, have difficulty maintaining nutrition other than by HPN and a medical doctor has judged HPN as necessary. Specifically, 30,000 yen (US$340.40)/month is provided as a guidance and management fee, 20,000 yen (US$226.90)/month when a fluid administration set is used and 12,500 yen (US$141.80) when an infusion pump is used.

For HEN

Among patients who are unable to tolerate oral intake or have difficulty with oral intake due to various causes, home enteral nutrition (HEN; elemental diet by tube feeding) is a method of nutrition implemented by patients themselves at home. Items providing clearly nutritional components (amino acids, dipeptides, tripeptides mainly as proteins; not including indigestible proteins) are eligible for reimbursement. These patients, regardless of the causative disease, have difficulty maintaining nutrition other than by HEN and a medical doctor has judged HEN as necessary. Specifically, 25,000 yen (US$283.60)/month is a guidance and management fee, 20,000 yen (US$226.90)/month for when a fluid administration set is used and 12,500 yen (US$141.80) for when an infusion pump is used.

Status of HPN Use in Japan

Trends in use of HPN and HEN

According to excerpts from medical reimbursement fee statistics by the Ministry of Health, Labour and Welfare (a 1-month period during June each year) (http://www.e-stat.go.jp/SG1/estat/GL02020101.do), in 2002, 5344 patients/month were using HPN in Japan. With an increase in enteral nutrition in response to the rapid spread of nutrition support teams (NSTs) in Japan, these figures decreased to 2240 patients/month in 2006 and 1680 patients/month in 2008. However, this trend reversed with an increase to 3962 patients/months in 2009 and widespread use in 7412 patients/month in 2011. HEN was used by 4856 patients/month in 2002, steadily increased to 6847 patients/month in 2006 and 7715 patients/month in 2008, and reached 10,125 patients/month in 2011. These figures suggest a steady promotion of home medical care by NST members, because the number of NSTs has been increasing; in 2013, there were more than 1700 (>20% of total number of hospitals) in Japan (Higashiguchi, 2011).

Use of HPN by age group

Among the 7412 patients using HPN during a 1-month period in June 2011, the breakdown by age groups was: 0–19 years, 164 (22.1%); 20–39 years, 232 (31.3%); 40–59 years, 3222 (43.5%); 60–79 years, 2462 (33.2%); and ≥80 years, 1332 (18.0%). The highest use of HPN was in middle-aged adults (40–59 years old), but a high 18.0% of the total represented elderly patients at least 80 years of age. This is a distinct feature in Japan.

Diseases in which HPN is used, HPN duration and return to society

Surveys on diseases in which HPN is used and patient return to society have not been conducted since 2000 in Japan. In a survey of 355 patients in 2000, HPN was most often used for malignant diseases, in 202 patients (56.9%). Only 12% of patients with malignant diseases returned to society, and mean duration of HPN use was short (139 days). Some 153 patients with benign diseases such as inflammatory bowel disease, ischaemic bowel disease and bowel motility disorders received HPN. A relatively high rate of about 60% of these patients returned to society. The mean duration of HPN was long (1969 days). Sixty-nine patients (19.4%) had SBS and 65% returned to society (Table. 7.1) (Takagi, 2003).

Major disease indications for HPN in Japan

SBS

SBS is also defined in Japan as a condition in which intestinal absorption is decreased due to intestinal resection or dysfunction of the residual intestine; and in which the required intake of fluids, electrolytes, major nutrients, trace elements and vitamins cannot be achieved using standard oral intake or enteral nutrition.

CAUSATIVE DISEASES There are various causative diseases, but large-scale detailed surveys on their incidence have not been conducted in Japan. Vascular disorders

Table 7.1. HPN implementation and return of patients to society. (From Takagi, 2003.)

Disease	Number of patients	Number returning to society (%)	Mean number of days of HPN
Overall	355	115 (32)	855
Malignancies	202	25 (12)	139
Benign diseases	153	88 (59)	1969
Inflammatory bowel disease	36	24 (67)	1888
Ischaemic bowel disease	38	28 (74)	2616
Bowel motility disorder	34	23 (68)	2170
Others	45	15 (33)	1337
Short bowel syndrome	69	45 (65)	–

of the intestine include: SMA (superior mesenteric artery) occlusion, SMV (superior mesenteric vein) occlusion, small bowel torsion, strangulation ileus, incarcerated hernia and intussusception. Inflammatory diseases of the intestine include: Crohn's disease, intestinal Behçet's disease, intestinal tuberculosis and intestinal ulcers. Other causes include tumours, trauma, adhesion ileus and proximal intestinal fistulas. However, SMA occlusion is the most common cause of SBS, accounting for about 40% of cases in Japan (Hatakeyama, 1993).

CRITERIA Massive resection of the small bowel in Japan is defined as up to 75 cm of residual intestine in children, up to 150 cm of residual intestine in adults or generally up to one-third the residual intestine (Takagi and Okada, 1996).

CLINICAL COURSE AND NUTRITIONAL MANAGEMENT The clinical course after small bowel massive resection is divided into three periods (Koyama *et al.*, 1984). Nutritional management corresponding to each period (Table 7.2) is required.

Period I (immediate post-operative period). This period is further divided into paralytic ileus (2–7 days post-operatively (PO)) and increased intestinal peristalsis (3–4 weeks PO). During paralytic ileus, attention must be paid to fluid and electrolyte management. During increased intestinal peristalsis, watery diarrhoea frequently occurs. Because this can easily lead to loss of all nutrition, particularly electrolytes, TPN is required for at least a month in many patients. In patients with normal nutritional status, energy (calories) can gradually be increased starting on day 2–3 PO, aiming at about 40 kcal/kg body weight/day. Amino acids (1–1.5 g/kg body weight/day), fats at about 20–30% of total calories, multivitamins and trace element preparations should also be given. Watery diarrhoea requires long-term control. If an anti-diarrhoea drug such as loperamide (4–16 mg/day) proves ineffective, a prescription narcotic anti-diarrhoea drug should be given. In addition, an H2 blocker or proton pump inhibitor will reduce gastric secretions and is useful to reduce diarrhoea.

Period II (recovery and adaptation period; a few months to 12 months PO). During the recovery and adaptation period, because absorption from the residual intestine improves and the frequency of watery diarrhoea gradually decreases, enteral

Table 7.2. Nutritional management after extensive small bowel resection. (From Koyama *et al.*, 1884.)

Period	Calories (kcal/kg body weight/day)	Residual intestine (cm)			
		0	~30	30–70	≥70
I	40–50	TPN	TPN	TPN	TPN
II	30–40	TPN	TPN	TPN	ED
		Home TPN	ED	LRD	LRD
			Home TPN	Home TPN	Normal diet
			Home ED	Home LRD	
II	30–50	Home TPN	Normal diet	Normal diet	Normal diet
			Home ED	Home ED	
			Home LRD	Home LRD	

ED, elemental diet; LRD, low-residue diet.

nutrition is started. From the perspective of reducing diarrhoea associated with decreased pancreatic enzyme activity and fat malabsorption, an elemental diet is often started in Japan. However, elemental diets have high osmotic pressure, which can lead to abdominal symptoms that include diarrhoea. Dilution of an elemental diet and a slower rate of administration when starting may be necessary. In addition, an elemental diet can lead to a deficiency in essential fatty acids, so periodic intravenous administration of lipid emulsions is necessary. While the clinical course is monitored, an elemental diet can be switched to a low-residue diet if possible, with the goal of transition to oral intake.

Period III (stabilized period; for a few years after period II). The compensatory level of the residual intestine has reached near maximum, so symptoms like diarrhoea are controlled. The goal in this period is weaning from TPN while stabilizing enteral nutrition and oral intake. In patients requiring an elemental or low-residue diet, HEN can be started. In patients unable to be weaned from TPN, HPN can be started.

COMPLICATIONS IN NUTRITIONAL MANAGEMENT SBS patients require long-term nutritional management and careful attention must be paid to metabolic complications. Iron is mainly absorbed from the duodenum, so excess supplementation is not necessary. However, if iron absorption is decreased due to bleeding from marginal ulcers or duodenal mucosal injury, iron deficiency anaemia can develop. Malabsorption of bile acids necessary for absorption of fats and fat-soluble vitamins can lead to vitamin D deficiency, abnormal calcium metabolism, abnormalities in trace elements (e.g. zinc, manganese, copper) and bone disorders (osteomalacia and osteoporosis). Malabsorption of bile acids also diminishes the bile acid pool, with an increase in gallstone formation.

Mild liver dysfunction is a frequent complication in TPN patients. However, particular attention is required in SBS patients, because progressive intrahepatic cholestasis and hepatic fibrosis can become life-threatening. Periodic monitoring is also necessary so that patients do not become deficient in major nutrients such as amino acids or in vitamins or electrolytes.

End-stage cancer

INDICATIONS The use of TPN in palliative care for end-stage cancer is fairly common in Japan. In Japan, it is gradually being understood that palliative care should be introduced not only for end-stage cancer, but also during all cancer treatment. When TPN is considered in patients with recurrent cancer, oral intake has become difficult and malnutrition is either present or anticipated. Specific instances include: (i) malnutrition due to adverse events with cancer treatment (e.g. chemotherapy, radiotherapy, surgery); (ii) gastrointestinal obstruction due to cancer; (iii) gastrointestinal dysfunction associated with ascites and carcinomatous peritonitis; and (iv) cancer cachexia. In particular, for cancer cachexia, a global consensus has emerged that artificial feeding, including TPN, is not indicated. In Japan, nutrition is often managed as described in the following section.

CLINICAL COURSE IN END-STAGE CANCER PATIENTS (CACHEXIA) The European Society for Parenteral and Enteral Nutrition (ESPEN) in 2010 proposed that cachexia be

classified in three stages: (i) pre-cachexia; (ii) cachexia; and (iii) refractory cachexia. The stage before cachexia when metabolic abnormalities are mild and no obvious cachectic symptoms are present is called 'pre-cachexia' (Muscaritoli *et al.*, 2010). Meanwhile, end-stage cachexia, when metabolic abnormalities are severe and nutritional status is unlikely to improve even with nutritional support, is called 'refractory cachexia' (Fearon *et al.*, 2011). Appropriate nutritional support is now considered important when there is little progression of cachexia; in other words, at a stage when metabolic abnormalities are mild (Arends *et al.*, 2006; Bozzetti *et al.*, 2009). With nutritional support started at this stage, development of malnutrition can be delayed, malnutrition due to other causes can be improved and tolerance to anticancer therapy can be increased.

In patients in Japan with recurrent or end-stage cancer, but not refractory cachexia, metabolic and nutritional management is basically similar to nutritional management in other patients. However, end-stage patients eventually develop irreversible metabolic changes, which then clearly result in reduced energy consumption (Fig. 7.1) (Higashiguchi, 2008). At this point in time, a down-shift in fluid and nutritional management is appropriate. Therefore, 'Guidelines for fluid and nutritional management in end-stage cancer patients' with a 'down-shift' based on whether refractory cachexia is present have been proposed (Higashiguchi *et al.*, 2004).

FLUID AND NUTRITIONAL MANAGEMENT IN CANCER PATIENTS *Pre-cachexia and cachexia.* Nutritional management in patients without refractory cachexia generally involves the supply of energy (calories) and nutrients that are neither excessive nor deficient. Oral intake should first be considered, with enteral and parenteral nutrition only when necessary.

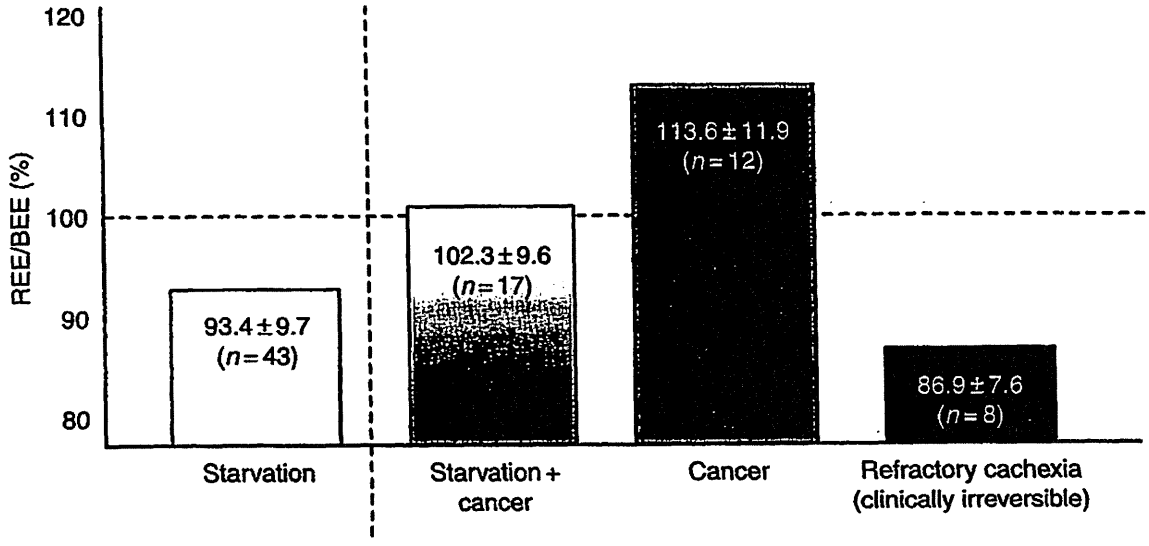

Fig. 7.1. Energy consumption and cancer progression (REE/BEE, resting energy expenditure/basal energy expenditure). (From Higashiguchi, 2008.)

1. Fluid administration: 30–40 ml/kg body weight/day (about 35 ml/day/kg body weight). Note, for end-stage patients: 25–35 ml/kg body weight/day (about 30 ml/day/kg body weight).
2. Required calories (kcal/day): basal energy expenditure (BEE) × activity factor (AF) × stress factor (SF). BEE (kcal/day) is calculated using the Harris–Benedict equation:

Males: 66 + (13.7 × weight in kg) + (5.0 × height in cm) − (6.8 × age in years).

Females: 655 + (9.6 × weight in kg) + (1.7 × height in cm) − (4.7 × age in years).

AF adjusts for the patient's physical activity. Physical activity is the component of energy expenditure under the control of the individual. For hospitalized patients, however, physical activity is limited, so a simple adjustment for activity is recommended in Japan (Long *et al.*, 1979): AF = 1.0 for bedridden patients and AF = 1.2 for ambulatory patients. SF adjusts for metabolic stress. Many hospitalized patients are hypermetabolic, so a simple adjustment for metabolic stress is recommended in Japan based on organ failure (SF = 1.2, 1.4 or 1.6 if one, two or three organs have failed), body temperature (37°C, SF = 1.2; 38°C, SF = 1.4; 39°C, SF = 1.6) and the presence of major burns (SF = 1.5–2.0).
3. Amount of amino acids (protein) (g/day): weight (kg) × stress factor (SF); including essential amino acids.
4. Amount of fats (g/day): 20–50% of required calories × 1/9 (0.5–1.0 g/kg body weight); including essential fatty acids. Rate of fat administration in parenteral nutrition is 0.1–0.2 g/kg body weight/h.
5. Amount of carbohydrates (g/day): required calories − (amount of amino acids) − (amount of fats). Non-protein calories/nitrogen (NPC/N) is 150–200 kcal/day; 300–500 kcal/day in patients with renal insufficiency.
6. Amount of vitamins and trace elements: daily required amounts.

Refractory cachexia. In patients with clinically apparent refractory cachexia, excessive fluids and energy (calories) should be reduced and the impact on remaining physical function should be controlled.

In Japan, patients able to maintain oral intake should be allowed to eat foods that they like and are able to eat. The following preparations are recommended with the understanding and consent of the patient: (i) vitamins and trace element preparations; (ii) high-fat high-protein nutrition in patients with lung metastases and respiratory insufficiency; (iii) glutamine, soluble fibre and oligosaccharides (GFO®) (Higashiguchi *et al.*, 2009) in patients with poor food intake, decreased immune function or who are receiving narcotics; and (iv) branched-chain amino acids in patients with muscle atrophy or limb weakness (Higashiguchi *et al.*, 2010).

In patients unable to tolerate oral intake, the wishes of the patient and family should be given first priority.

1. Fluid administration: 15–25 ml/kg body weight/day (about 20 ml/day/kg body weight; 500–1000 ml/day). Thirst (dry mouth) should be prevented not only by intravenous fluids, but also by oral care and green tea spray.

2. Required calories (kcal/day): 5–15 kcal/kg body weight/day (about 200–600 kcal/day).
3. Nutrients: (i) primarily carbohydrates; and (ii) amino acids (branched-chain amino acids), with small amounts of essential fatty acids when necessary.
4. Vitamins and trace elements: required daily amounts to prevent stomatitis and decubitus ulcers.

Fluid and nutritional management according to these standards can minimize suffering from end-stage symptoms, improve QoL and help patients to achieve a peaceful death.

Conclusion

The indications for HPN in Japan are generally the same as the indications for TPN in hospitalized patients. However, it is important for HPN that a patient's clinical symptoms and condition be stable and that nutrition be managed in a setting where the need for emergency measures will be unlikely. Careful evaluation during hospitalization and regular monitoring of the patient's clinical symptoms and condition when receiving HPN are therefore necessary.

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References

Arends, J., Bodoky, G., Bozzetti, F., Fearon, K., Muscaritoli, M., Selga, G., van Bokhorst-de van der Schueren, M.A., von Meyenfeldt, M.; DGEM (German Society for Nutritional Medicine), Zürcher, G., Fietkau, R., Aulbert, E., Frick, B., Holm, M., Kneba, M., Mestrom, H.J., Zander, A.; ESPEN (European Society for Parenteral and Enteral Nutrition) (2006) ESPEN Guidelines on Enteral Nutrition: non-surgical oncology. *Clinical Nutrition* 25, 245–259.

Bozzetti, F., Arends, J., Lundholm, K., Micklewright, A., Zurcher, G. and Muscaritoli, M.; ESPEN (2009) ESPEN Guidelines on Parenteral Nutrition: non-surgical oncology. *Clinical Nutrition* 28, 445–454.

Fearon, K., Strasser, F., Anker, S.D., Bosaeus, I., Bruera, E., Fainsinger, R.L., Jatoi, A., Loprinzi, C., MacDonald, N., Mantovani, G., Davis, M., Muscaritoli, M., Ottery, F., Radbruch, L., Ravasco, P., Walsh, D., Wilcock, A., Kaasa, S. and Baracos, V.E. (2011) Definition and classification of cancer cachexia: an international consensus. *Lancet Oncology* 12, 489–495.

Hatakeyama, K. (1993) Short bowel syndrome. In: Ogoshi, S. (ed.) *Manual for Fluid and Nutritional Management*. Igakusyoin, Tokyo, pp. 119–128.

Higashiguchi, T. (2008) Nutritional management for cancer cachexia. *Japanese Journal of Clinical Nutrition* 113, 602–607.

Higashiguchi, T. (2011) Where are we standing in all over the world, considering about the development of medical system for nutritional therapy. *Journal of Japanese Society for Parenteral and Enteral Nutrition* 26, 5–10.

Higashiguchi, T., Ito, A., Murai, M. and Iida, T. (2004) Nutritional management for terminally cancer patients. *The Japanese Journal of Medical Society* 132, 61–64.

Higashiguchi, T., Ito, A., Futamura, A., Kodama, Y., Sadamaoto, T., Murai, M., Shibata, K., Kaneko, T., Tomatsu, A., Chihara, T., Shinpo, H., Miki, S., Yamaguchi, M., Hino, K. and Kondo, Y. (2009) Effect of glutamine–fiber–oligosaccharide (GFO) on the pathological and functional changes in the intestinal mucosa associated with total parenteral nutrition in rats. *Japanese Journal of Surgical Metabolism and Nutrition* 43, 51–60.

Higashiguchi, T., Futamura, A. and Ito, A. (2010) Effect of a complementary nutrition diet for improving clinical condition and function in terminal cancer patients: a controlled clinical trial. *Japanese Journal of Surgical Metabolism and Nutrition* 44, 157–169.

Koyama, M., Hatakeyama, K. and Yamadera, Y. (1984) Metabolism and management after massive intestinal resection. *Surgical Therapy* 51, 43–50.

Long, C.L., Schaffel, N., Geiger, J.W., Schiller, W.R. and Blakemore, W.S. (1979) Metabolic response to injury and illness: estimation of energy and protein needs from indirect calorimetry and nitrogen balance. *JPEN Journal of Parenteral and Enteral Nutrition* 3, 452–456.

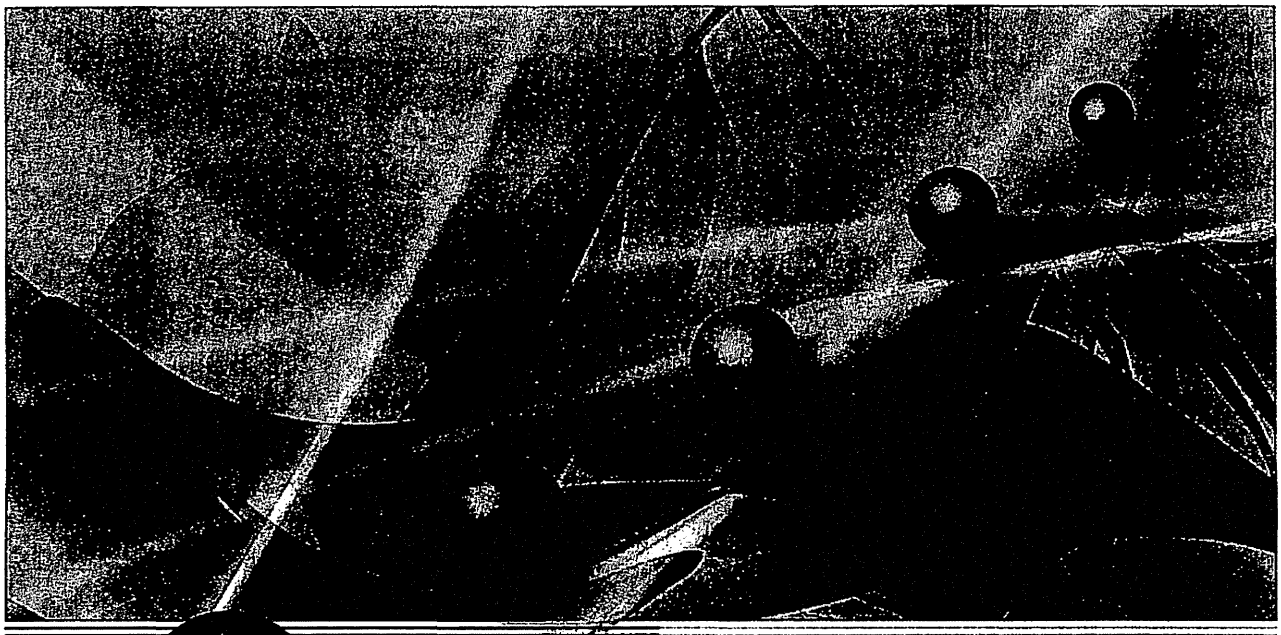
Muscaritoli, M., Anker, S.D., Argilés, J., Aversa, Z., Bauer, J.M., Biolo, G., Boirie, Y., Bosaeus, I., Cederholm, T., Costelli, P., Fearon, K.C., Laviano, A., Maggio, M., Rossi Fanelli, F., Schneider, S.M., Schols, A. and Sieber, C.C. (2010) Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by special interest groups (SIG) 'cachexia-anorexia in chronic wasting diseases' and 'nutrition in geriatrics'. *Clinical Nutrition* 29, 154–159.

Onodera, T. (2001) The guidelines for home parenteral nutrition. In: Prompting Institute of Total Health (ed.) *Prerequisites for Implementation, Indications, and Contraindications for Home Parenteral Nutrition.* Bunkodo, Tokyo, pp. 1–8 (in Japanese).

Shirotani, N. (2006) Home parenteral nutrition. In: Japanese Society for Parenteral and Enteral Nutrition (ed.) *Guideline of Parenteral and Enteral Nutrition.* Nankodo, Tokyo, pp. 25–28.

Takagi, Y. (2003) Home parenteral and enteral nutrition in Japan – present and future. *Japanese Journal of Gastroenterology* 100, 819–828.

Takagi, Y. and Okada, A. (1996) Short bowel syndrome. *Clinical Digestive Medicine* 11, 495–502.



CACHEXIA AND SARCOPENIA

悪液質とサルコペニア

リハビリテーション栄養アプローチ

荒金英樹　若林秀隆　編著

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1. 悪液質とは

ポイント

○悪液質は慢性消耗性疾患をベースとして生じる，筋肉量の減少を主徴とした複合的な代謝異常の症候群で，身体機能の低下，生活の質の悪化，治療毒性の増強，予後の悪化をもたらす．
○慢性消耗性疾患における悪液質，およびがん悪液質の定義やステージ分類が発表され支持を集めつつあるが，診断基準はいまだ流動的である．
○進行した悪液質の段階で栄養状態を改善することは困難で，早期からの栄養サポートによる低栄養の予防が重要と考えられている．

定義

1．悪液質をめぐる歴史

悪液質はがんに限らず，呼吸不全や心不全などの慢性消耗性疾患においてみられる栄養不良の終末像で，衰弱した状態を指す言葉として古くから用いられてきた[1,2]．悪液質の主症状である体重減少，食思不振を伴う衰弱状態は，聖書や古代ギリシャの文献にも記載があるが[2]，悪液質を意味する英語“cachexia”は，ギリシャ語のkakós（bad）とhexis（condition）に由来し[3]，古くは紀元前1世紀のローマの医師の記述に登場している[1]．現在に至るまで多くの歴史上の人物が，がんなどの慢性消耗性疾患の進行とともに，悪液質と考えられる状況に陥ったことは，さまざまな歴史書のなかに描かれている[2]．

多くの疾患の治療成績が向上した現代医学において，慢性疾患における難治性の消耗状態である悪液質の克服が次第に強く求められるようになった．1970年代以降，高カロリー輸液をはじめ，種々の栄養療法が，進行がん患者の栄養不良の改善のため試みられてきたが[4-6]，通常の飢餓に対する効果とは異なり，悪液質に対しては必要エネルギーや栄養素を補う原則的な栄養療法では十分な成果をあげることができず，悪液質は種々の代謝異常を伴う，治療抵抗性の栄養不良の症候群で，飢餓とは異なる病態[3,7]であることが知られるようになった．

慢性消耗性疾患の栄養不良の進展に，炎症，インスリン抵抗性，蛋白・脂質分解などの代謝異常がみられることは比較的早くから専門家の間では認識されていた[8]が，悪液質の定義・診断基準は，体重減少や食思不振を中心に考えられてきた[2,9,10]．

2000年代に入り，筋肉量の減少[11]，種々の代謝異常[12]，難治性の栄養不良[13]，複雑な機序による症候群[14]などの表現を用いた悪液質の定義が報告されるようになったが，臨床現場と研究者に受け入れられる悪液質の明確な定義の欠如は，慢性消耗性疾患の栄養不良を指す言葉の混乱を招き，悪液質患者の治療や早期発見，治療方法のメタアナリシスなどの研究の障害となるため，世界規模で定義の必要性が叫ばれるようになった[7,15]．

2．慢性消耗性疾患における悪液質の定義

2006年末に米国ワシントンで行われた欧米のエキスパートによるCachexia Consensus Working Groupで，「悪液質は基礎疾患によって引き起こされ，脂肪量の減少の有無にかかわらず，筋肉量の減少を特徴とする複合的代謝異常の症候群である．臨床症状として成人では体重減少（体液貯留を是正して評価），小児では成長障害がみられる（内分泌疾患を除外して評価）．食思不振，炎症，インスリン抵抗性，筋蛋白分解を高頻度に認める．悪液質は飢餓，加齢による筋肉量の減少，うつ病，吸収障害や甲状腺機能亢進とは異なる病態で，疾患罹患率を増加させる」[7]と慢性消耗性疾患における悪液質の定義がなされ（以下，ワシントン定義），それまで混乱があった悪液質の概念を明確にした画期的なものとなった．

3．がん悪液質の定義

ワシントン定義ではがんに限らず慢性疾患全般を対象としていたため，他の慢性疾患に比較し経過が早いなどのがんの特性を考慮した悪液質の定義が求められるに至った．いくつかのがん悪液質の定義や診断基準が提唱され，2006年にFearonらは，①10%以上の体重減少，②1,500kcal/日未満の経口摂取，③全身の炎症反応，CRP>1.0 mg/dLの3項目をあげており[12]，2009年のSCRINIO Working Groupの10%以上の体重減少の有無と食思不振，早期満腹感あるいは倦怠感の有無による悪液質の状態の分類[1]が，それぞれ単施設での悪液質患者のデータに基づいたものとして報告されている．

その後，European Palliative Care Research Collaborative（EPCRC）から「がん悪液質とは，栄養療法で改善することは困難な著しい筋肉量の減少がみられ（脂肪量の減少の有無にかかわらず），進行性に機能障害をもたらす複合的な栄養不良の症候群で，病態生理学的には，栄養摂取量の減少と代謝異常によってもたらされる蛋白およびエネルギーの喪失状態である」[16]とがんの特性を考慮した“がん”悪液質についての定義（以下，EPCRCの定義）が提唱され，コンセンサスペーパー[16]とガイドライン[17]上で紹介された．この定義は，ステージ分類とともに広く利用され，わが国でも日本緩和医療学会「終末期癌患者に対する輸液治療のガイドライン（2013年版）」[18]をはじめ，がん悪液質の標準的な定義として用いられつつある．

4．悪液質の定義と診断基準

慢性消耗性疾患における悪液質の診断基準として，ワシントン定義では12カ月以内に5%以上の体重減少（あるいはBMI20kg/m^{2}未満）に（a）筋力低下，（b）疲労感，（c）食思不振，（d）除脂肪体重低値，（e）生化学データの異常値（1.CRP>0.5mg/dLあるいはIL-6>4.0pg/ml，2. Hb<12g/dL，3. Alb<3.2g/dL），の5項目中3項目以上がある場合としている（**図1**）[7]．また，2011年のEPCRCによるがん悪液質の診断基準

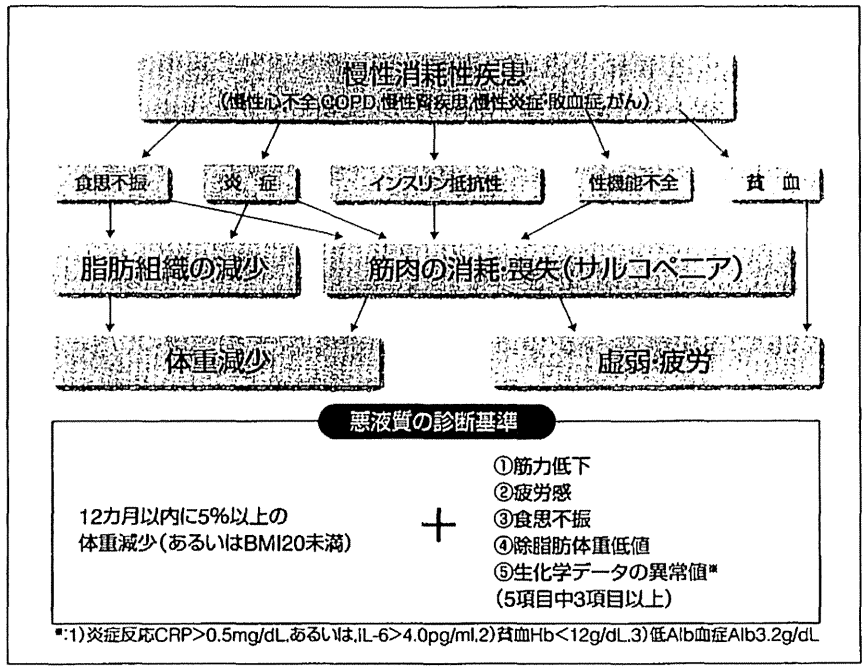

図1　悪液質の病態と診断基準　(Evans et al 2008)[7]

では，A. 6カ月間に5%以上の体重減少，B. BMI < 20kg/m^2 かつ2%以上の体重減少，C. 筋肉減少（サルコニペア）かつ2%以上の体重減少のいずれか[16]としている．

これらの基準は，同時に提唱された定義に基づき，発表されているが，診断基準に関しては議論も多く，確固たる生物学的指標の確立を含め，今後のさらなる検討が必要とされている．

5. わが国における悪液質の定義

わが国でもがんを対象に，悪液質の定義が発表されているが，2000年以降，東口らはがん悪液質を「がん進展に伴う蛋白代謝を主体とする高度の不可逆的な栄養障害，あるいは治療にても制御不能の全身浮腫，胸水，腹水をきたす病態」と定義し，この有無による緩和ケアの栄養サポートの方針（担癌・末期癌患者に対する輸液・栄養管理実施基準）をいち早く発表している[19]．2007年に日本緩和医療学会からが発刊された「終末期癌患者に対する輸液治療のガイドライン」では，「悪性腫瘍の進行に伴って，栄養摂取の低下では十分に説明されない，るいそう，体脂肪や筋肉量の減少が起こる状態」と記載され[20]，改訂された2013年版では，2011年に発表されたEPCRCの定義，ステージ分類が紹介・掲載されている[18]．

症候

1. 悪液質をもたらす疾患と病態

悪液質はがん，慢性心不全，慢性腎不全，慢性閉塞性肺疾患，自己免疫疾患，慢性の感染症・敗血症などの慢性消耗性疾患に伴いみられ[7]（表）[21]，異化亢進をもたらす代謝異常と，食思不振などによる安静時エネルギー摂取量の減少が複雑に関連して