Current Status Concerning Cancer-Cachexia Syndrome in Japan

~ Challenge to improve functional prognosis ~

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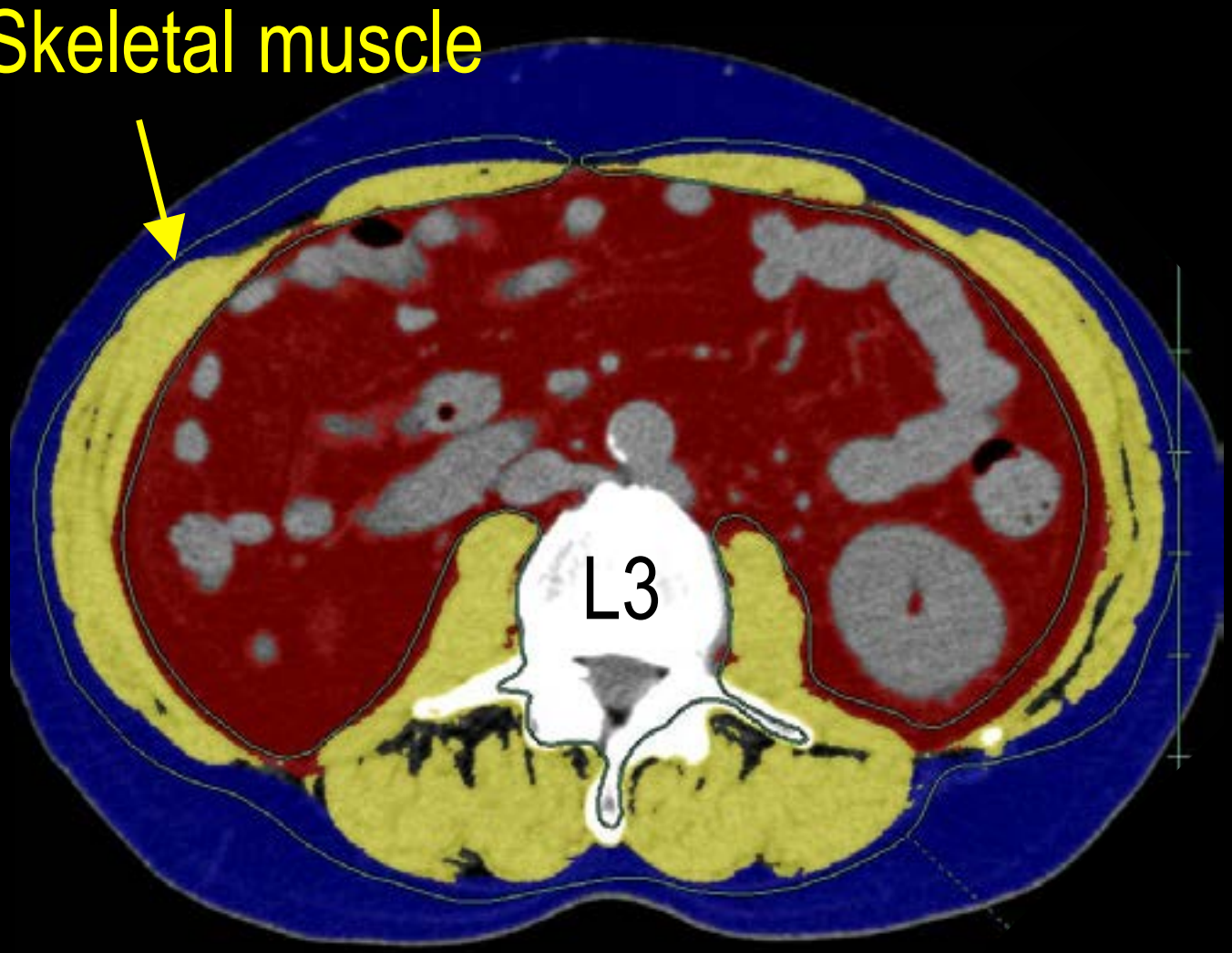
June 29, 2018 (Friday) in JASCC/MASCC joint session at Vienna

Faculty Disclosure

	No, nothing to disclose
X	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Ono pharmaceutics	x							

Body composition in advanced cancer patients



Lumbar CT at the time of diagnosis

73 y.o. man with advanced lung cancer & bone mets

Assessment

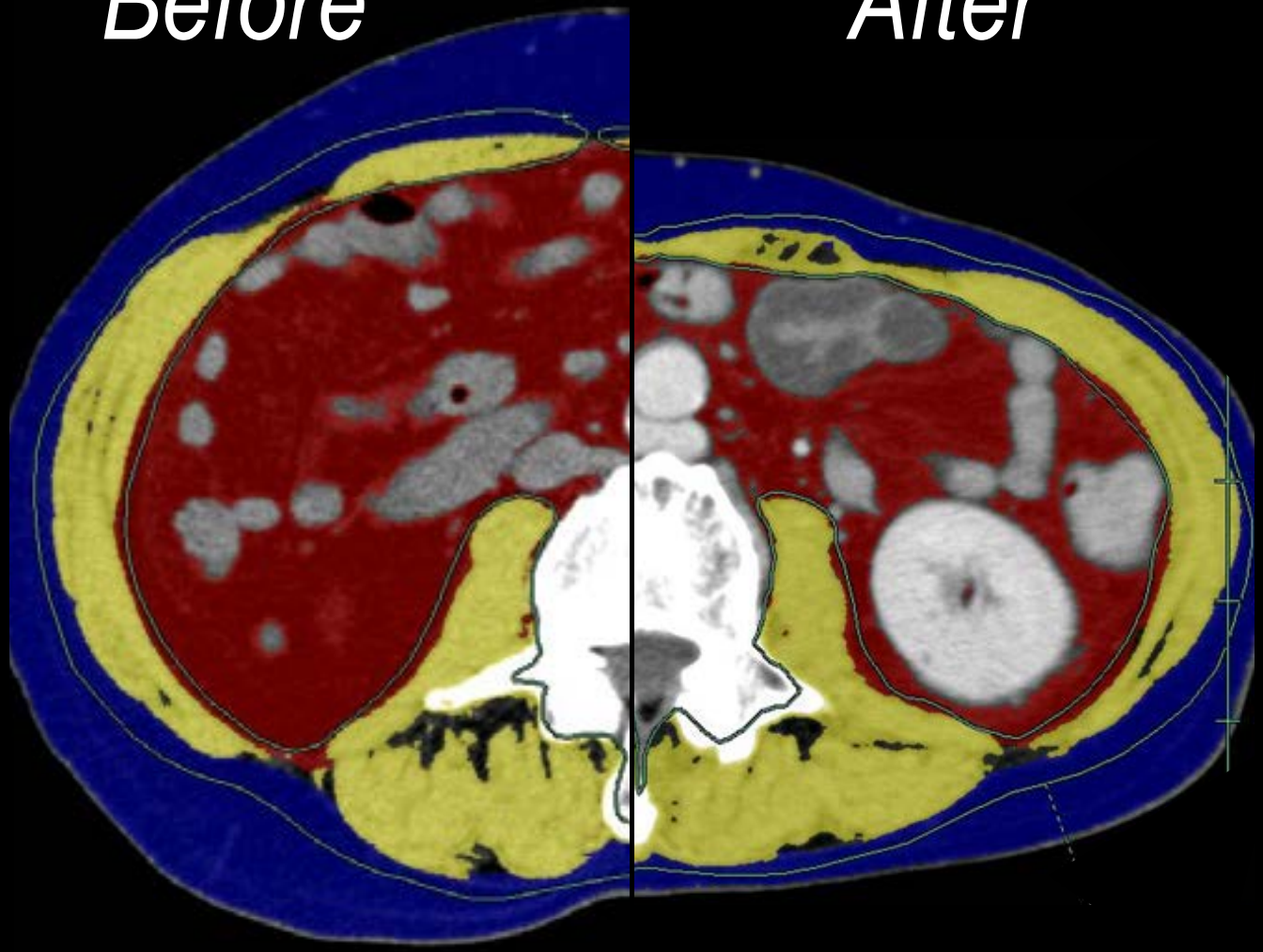
- Muscularity index 42 cm^2/m^2
  → *Muscle depletion*
- Weight loss (6mo) - 4.5%
  → *Cancer cachexia*

Cancer treatment

Palliative bone radiation & chemotherapy

What he lost in the next 6 months

Before *After*



Weight	- 11 kg
Lean body mass	- 7 kg
Hand-grip strength	- 4 kg
Walk distance	- 190 m
Barthel index	- 35 pts

HE NEEDED EXERCISE AND NUTRITION

Today’s Agenda

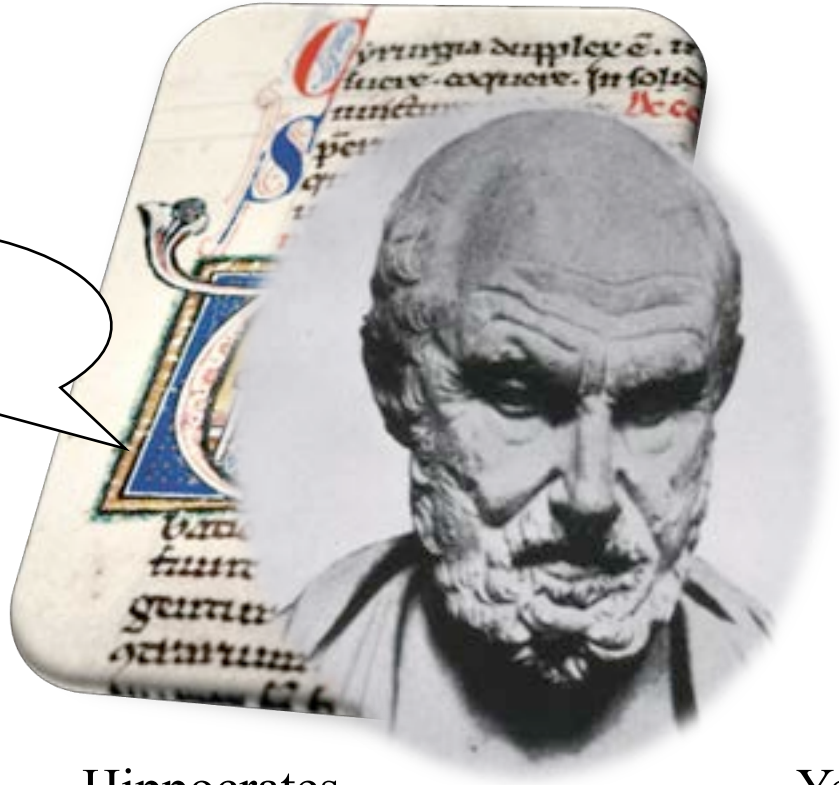
1. History of cachexia
2. Awareness in JAPAN
3. Functional prognosis of cancer cachexia
4. Introduction of the NEXTAC study

We recognized “cachexia” from ancient time

Ancient Greece

“κακόςἕξις”, Cachaxia

A sign of death

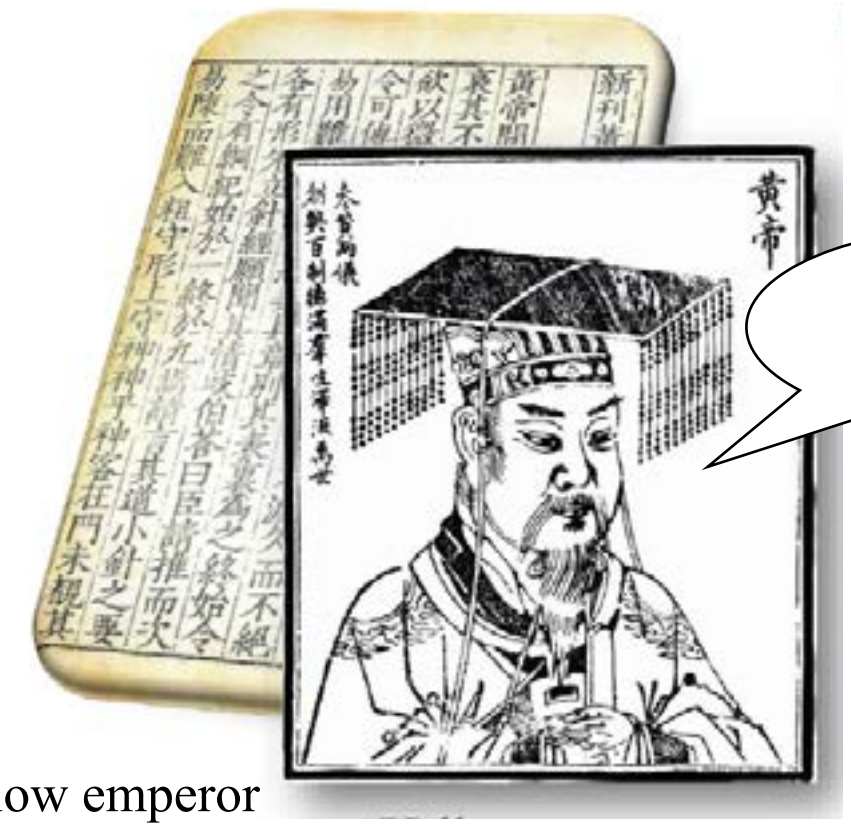


Hippocrates
460 BC – 370 BC

Ancient China

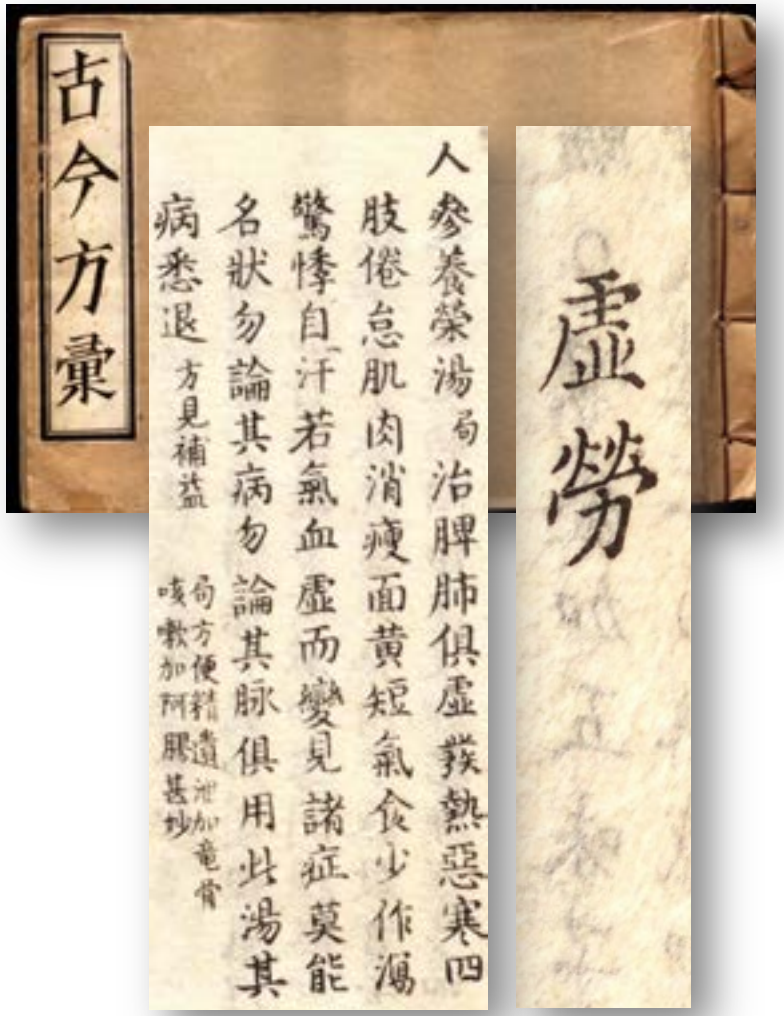
“萎病”: Atrophic illness

Functional prognosis



Yellow emperor
2000 BC

Katz AM. Br Heart J. 1962, Huang di naijin, 東洋学術出版社1995



"Kokonhoi", Tsugen Koga, 1692
National Institute of Japanese Literature

In Japan, it was called as "Weakness and Fatigue Disorder" (虚労)

Kyo-Rou

Definition

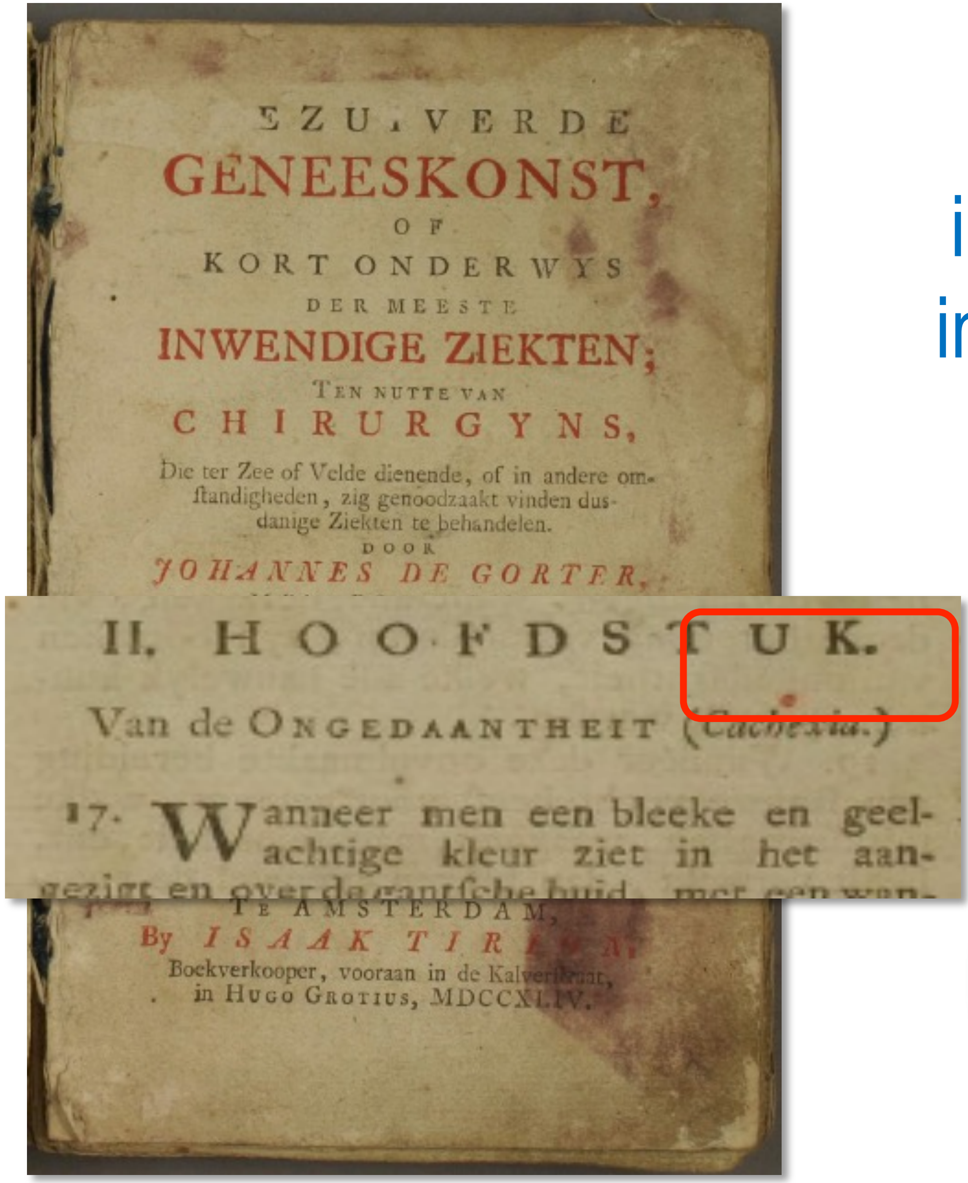
Wasting condition caused by a variety of chronic inflammatory diseases such as tuberculosis or parasitic disease.

Signs and Symptoms

- Anorexia & Fatigue
  - Emaciation
  - Depression
- Sedentary behavior

Treatments

Nutritional support & herbal medicines (e.g.Rikkunshito)

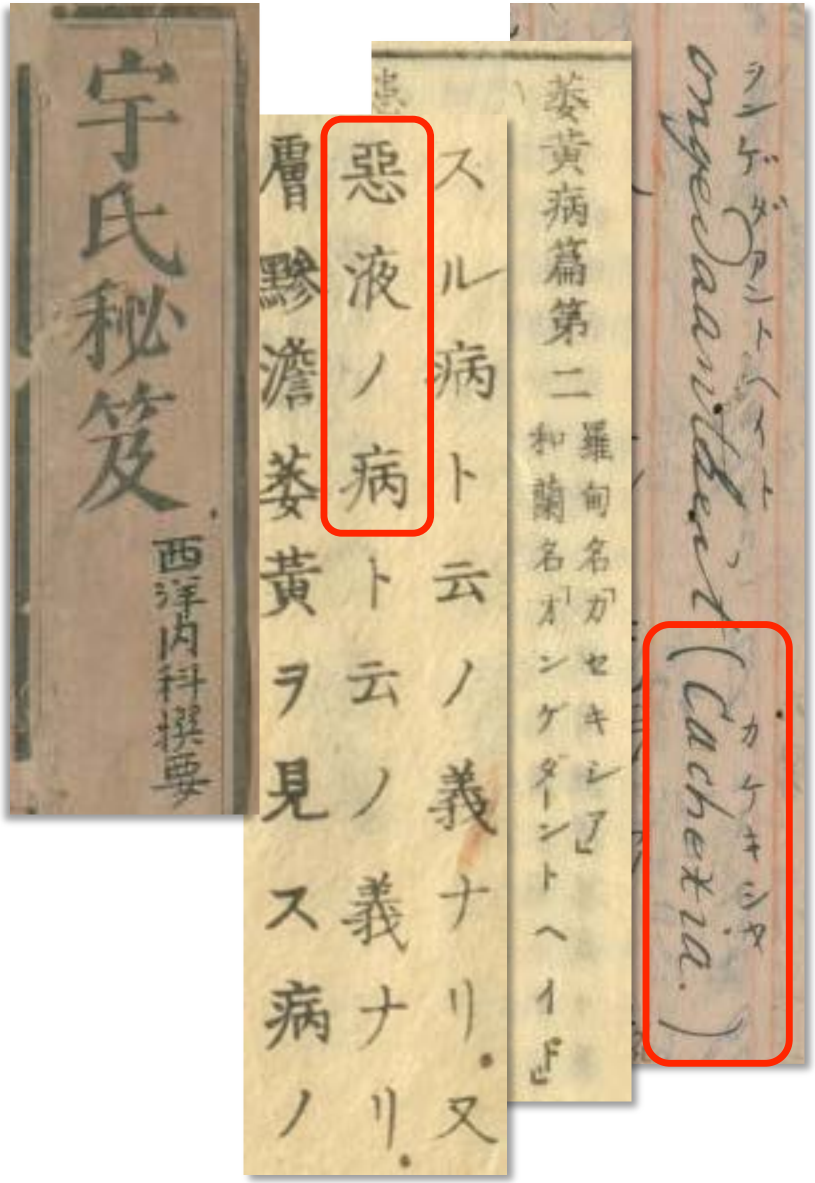


Simple Guideline on a Variety of Internal Disorders, Johannes de Gorter, 1744
Waseda University Library, Japan

"Cachexia" was imported to Japan in 18th century, the late Edo period

Translated

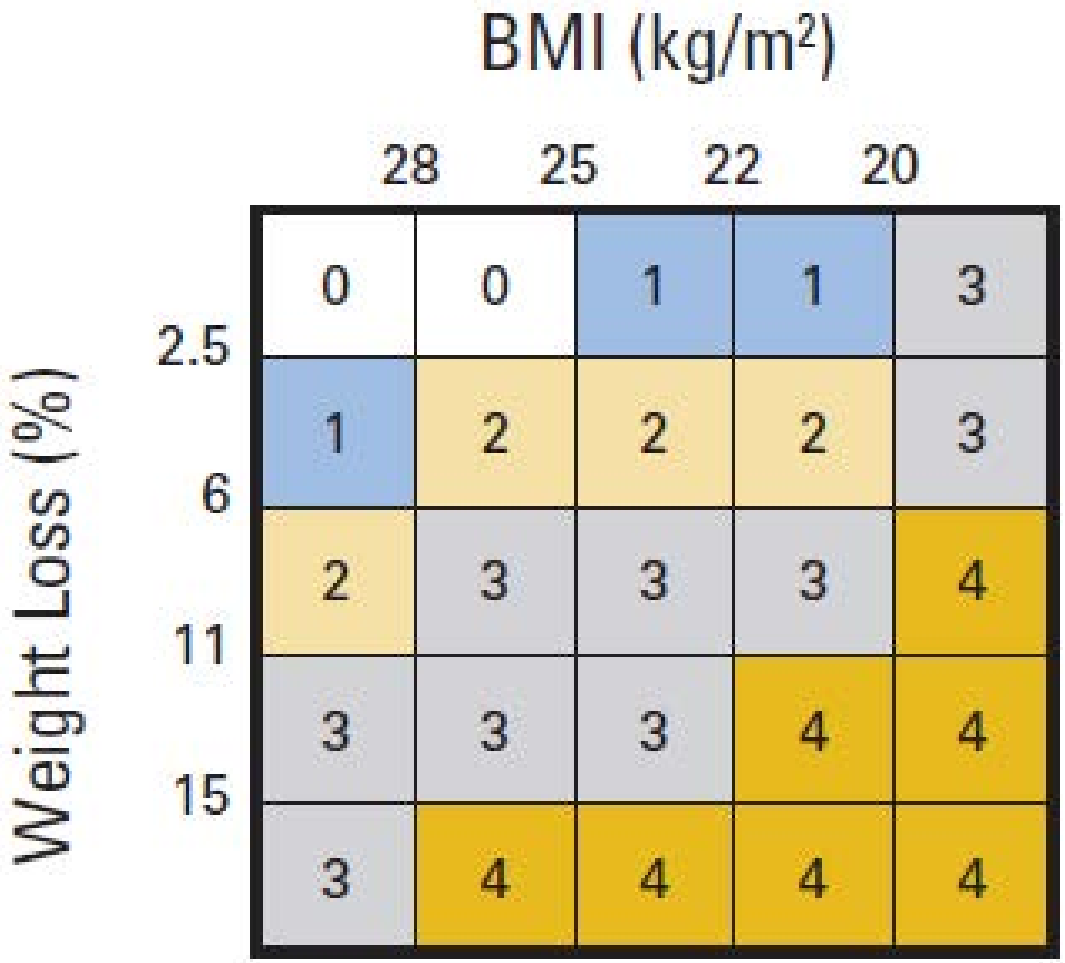
Utagawa Genzui (1756-1798)



Genzui's translation draft "Ushi Hikyu", 1793
National Diet Library, Japan

And today,

Cachexia was not yet overcome



Grade	Estimated Survival time
0	21 months
1	15 months
2	11 months
3	8 months
4	4 months

Martin L, J Clin Oncol. (2015)

After >2000 years, we still suffer from cachexia

- Decreased physical capacity[1,2]
- Poor QOL[2,3]
- Poor tolerance to cancer treatment[4]
- Easily disabled[7,8]
- Longer hospital stay[7,8]
- Higher medical cost[7,8]
- Shorter survival time[5,6]

Bruera E BMJ 1997, p1219

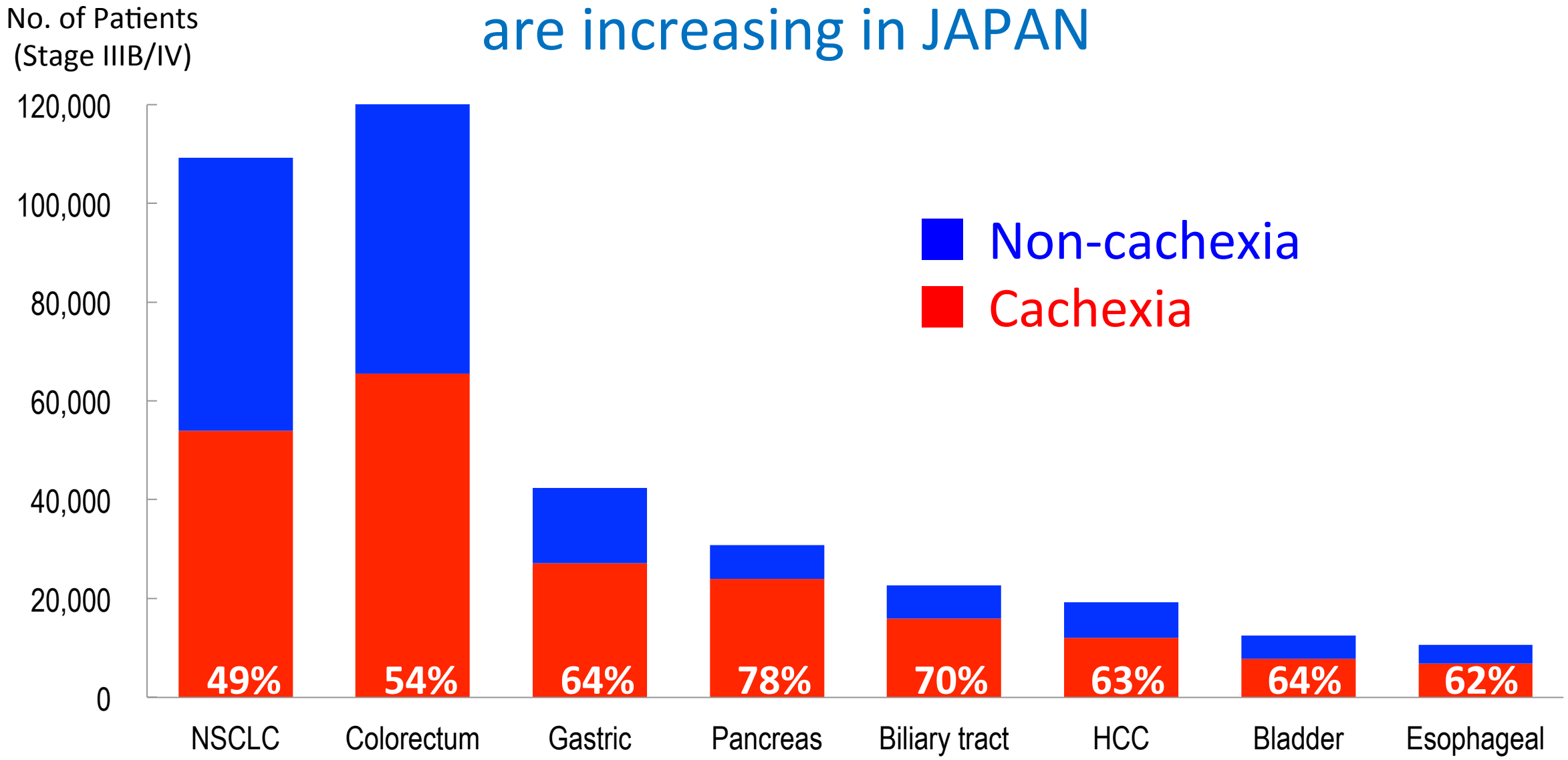
1. Naito T, BMC Cancer (2017, Aug)
2. Takayama K, Support Care Cancer (2016)
3. LeBlanc TW, JPSM (2004)
4. Ross PJ, Br J Cancer (2004)
5. Kimura M, Support Care Cancer (2014)
6. Fearon KCH, Am J Clin Nutr (2006)
7. Naito T, BMC Cancer (2017, Nov)
8. Arthur ST, J Med Econ (2016)

Today's Agenda

1. History of cachexia
2. Awareness in JAPAN
3. Functional prognosis of cancer cachexia
4. Trial of multimodal intervention
5. Introduction of the NEXTAC study

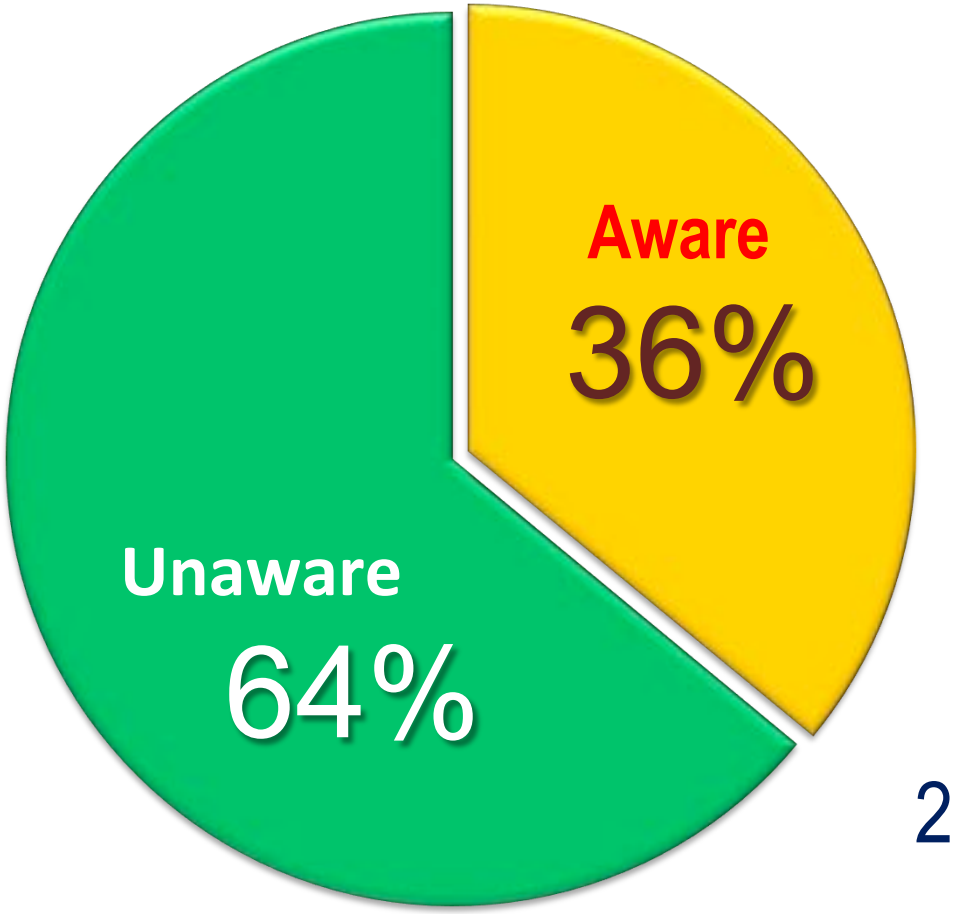
Hokusai, 1823

Number of patients living with advanced cancer & cachexia are increasing in JAPAN



Web-based survey in 2016, Copyright© 2018 IQVIA. Reprinted with permission

Physicians' Awareness of the diagnostic criteria of Cachexia in JAPAN



2016 survey in Japan

Web-based survey in 2016, Copyright© 2018 IQVIA. Reprinted with permission

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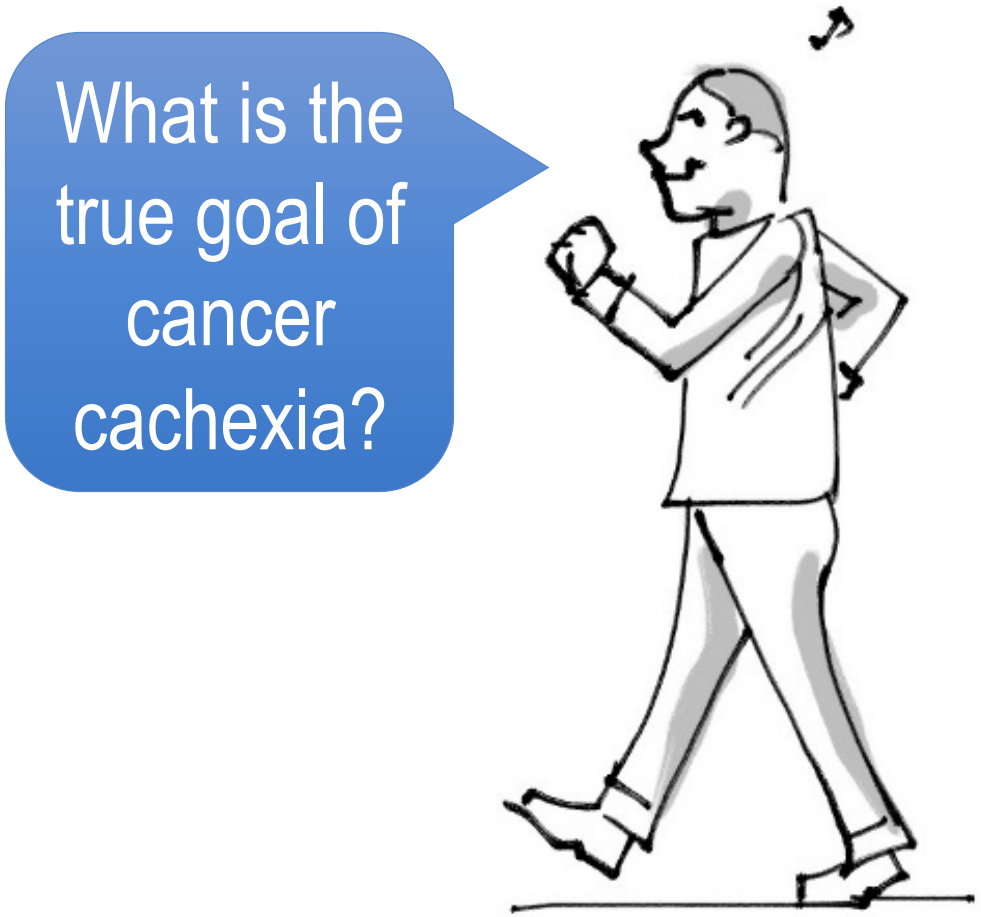


Preliminary prospective observational study for elderly with advanced NSCLC

- Patients: Advanced NSCLC (≥70 y.o)
  ECOG-PS 0-2
  Being to start chemotherapy
- Aim: To visualize functional prognosis
- Sample size: n=30
- Study period: 2013-2015
- Trial No: UMIN000009768

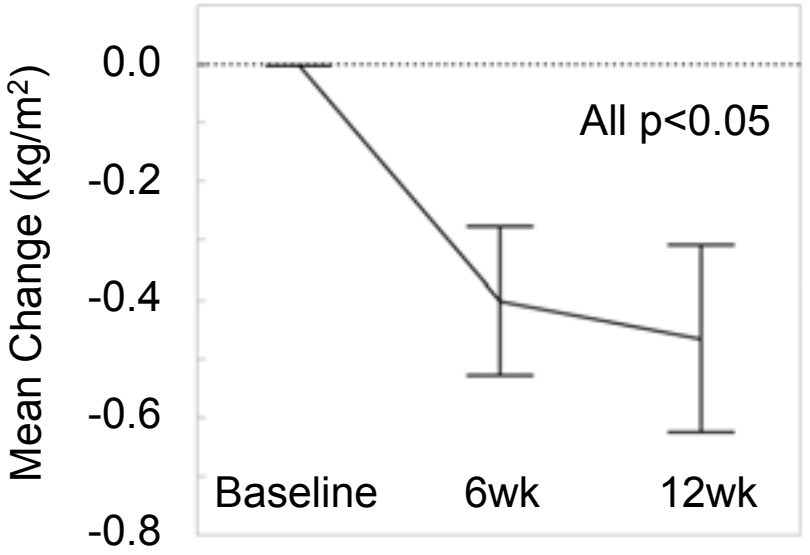
Characteristics	All (N=30)
Age (range)	**74** (70-82)
Gender (F:M)	11:19
Stage IV	29 (97%)
ECOG-PS 0-1	29 (97%)
Cytotoxic regimen	24
Targeted regimen	6
Cachexia	18 (60%)
Pre cachexia	7 (23%)
Muscle depletion	20 (67%)

83%

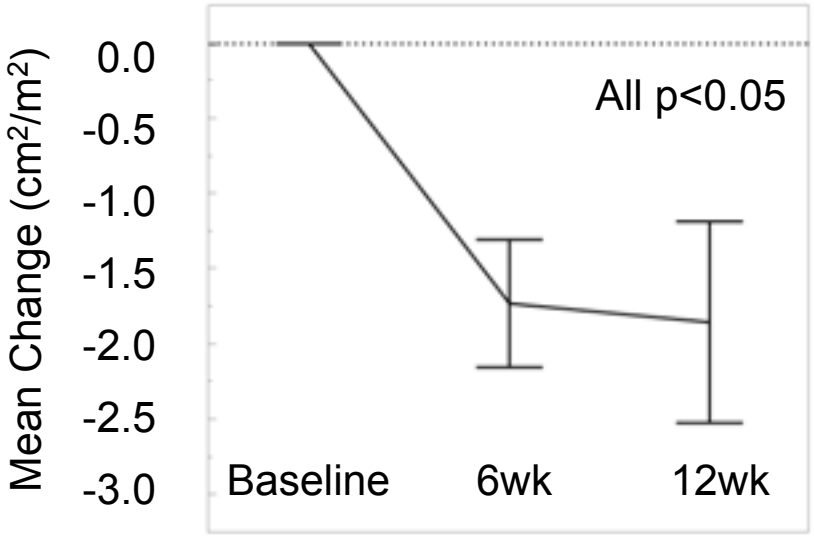
Naito T, BMC Cancer, 2017
MSCC 2015 @Miami

Longitudinal changes in physical parameters within 6-12 weeks from initiation of chemotherapy.

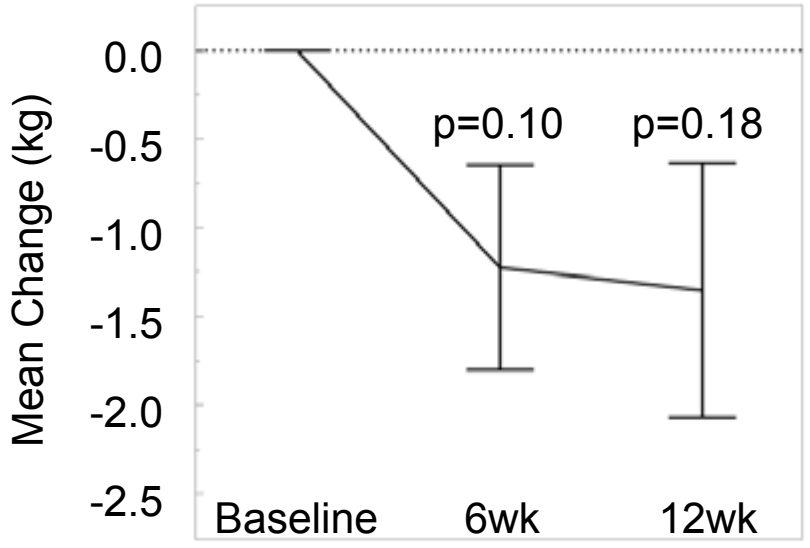
BMI



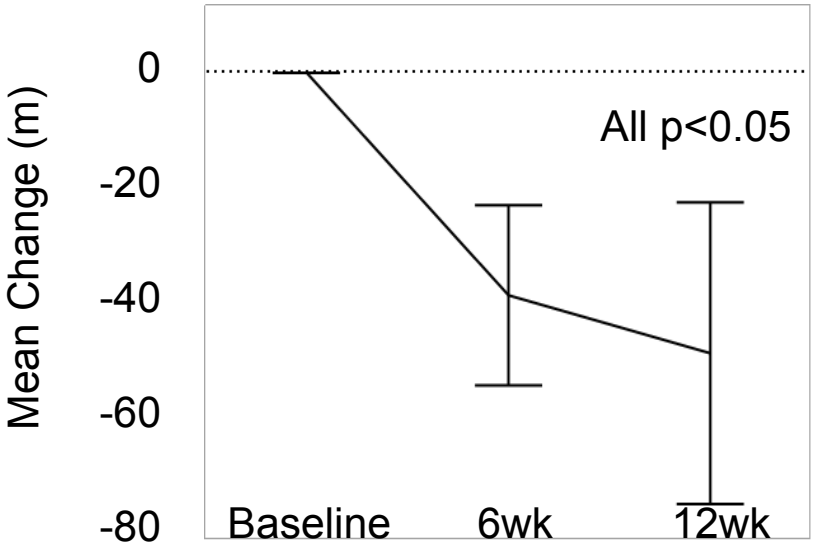
Muscularity index



Hand-grip strength

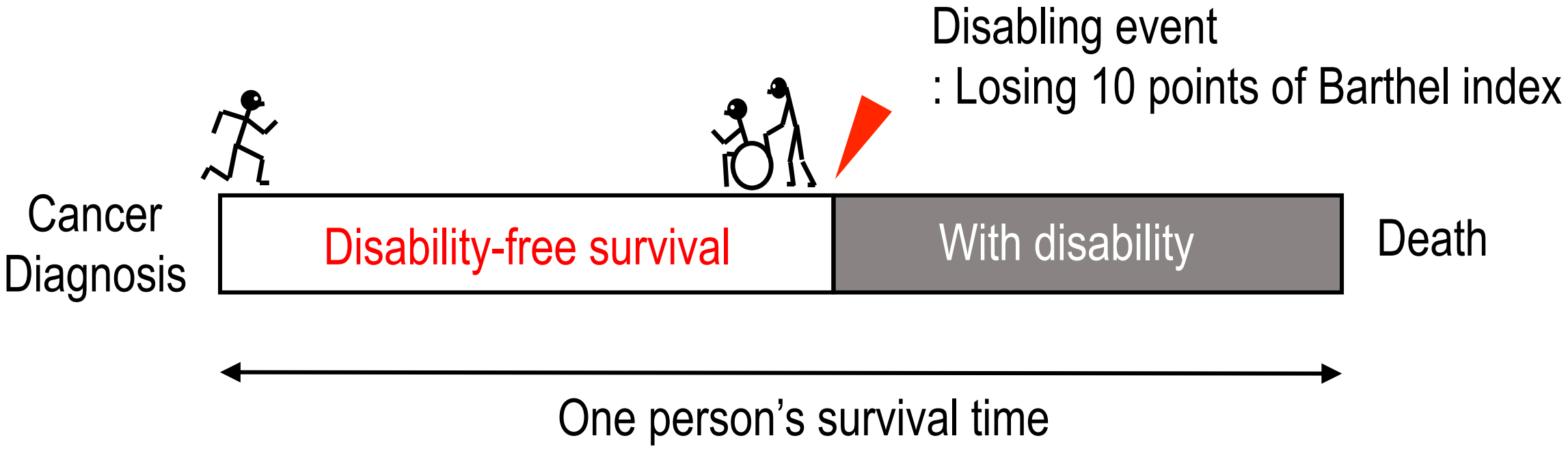


Shuttle walk distance

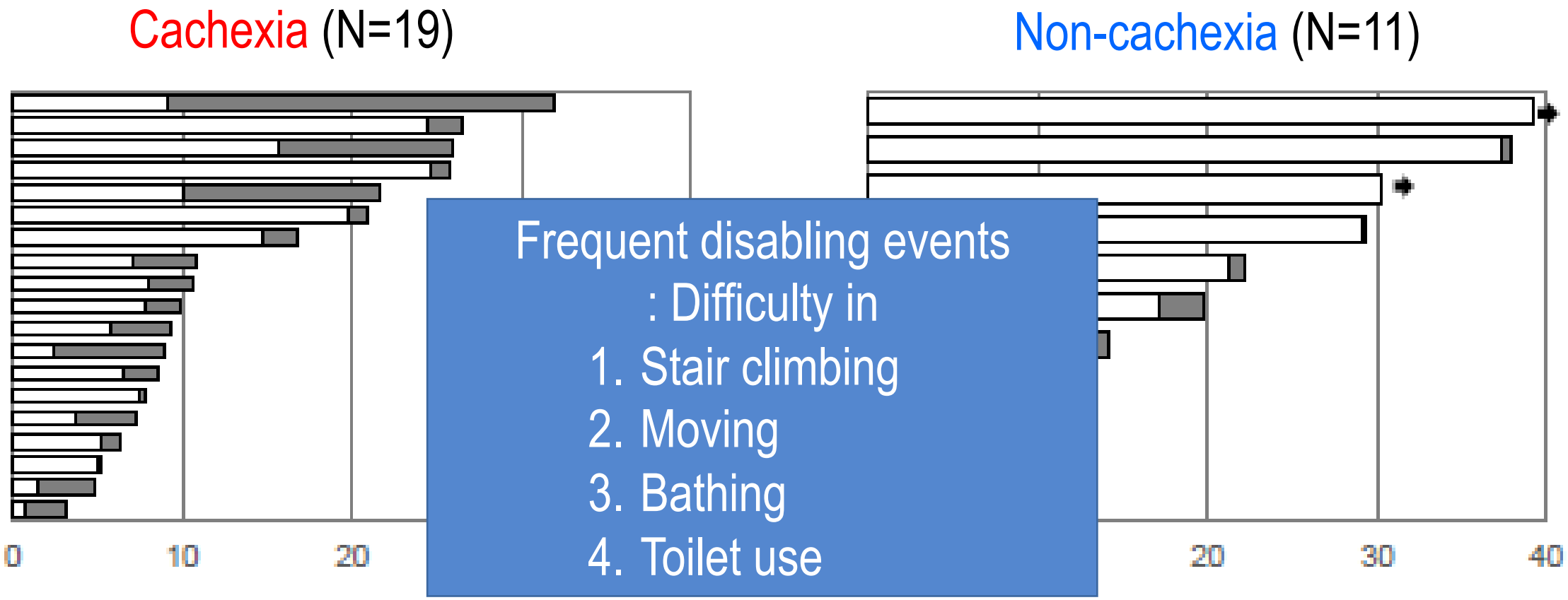


Naito T, BMC Cancer, 2017
MSCC 2015 Miami

Measuring functional prognosis



Cachectic patients easily develop disability



Disability-free survival: 8 vs 17 months (Log-rank p< 0.05)

Naito T, BMC Cancer, 2017
MSCC 2016 @Copenhagen

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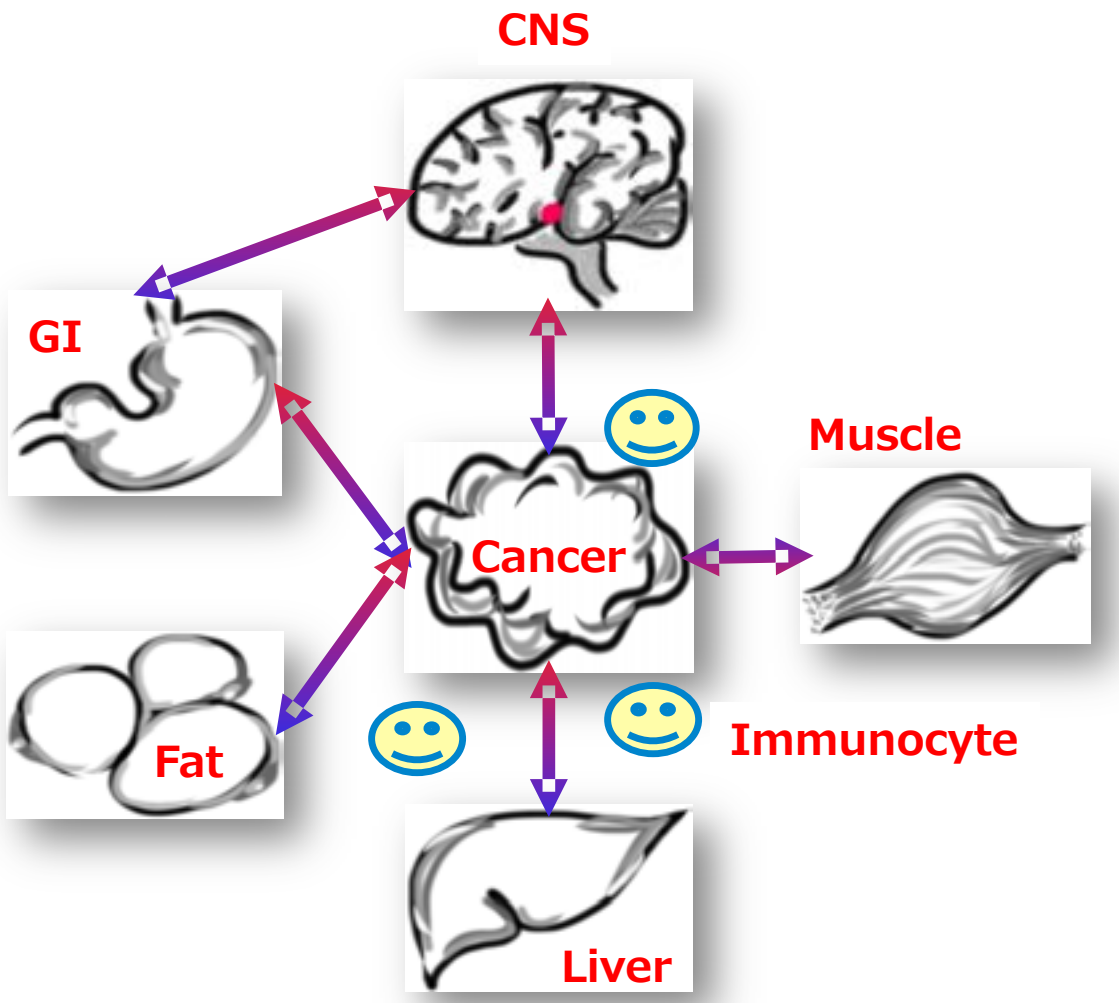
Cachexia is a multifactorial disease



Pre-MENAC study

Patients: Advanced pancreatic or non-small-cell lung cancer, KPS≥70

R
N=46

3 institutions from Norway and UK

1:1 ratio

Usual care n=21

Usual care + MENAC n=25

- Exercise (Home-based aerobic and resistance training)
- Nutrition (Counseling + Prosure®)
- NSAID (Celecoxib)

6 weeks

Number of interventions increases

Combinations	Compliance
Singe intervention	76% in NSAIDS
	60% in Exercise
	48% in Supplements
2 combinations	20 – 48%
3 combinations	12%

Solheim TS, Journal of Cachexia, Sarcopenia and Muscle, 2017

Nutritional and EXercise Treatment for Advanced Cancer - The NEXTAC program -

The JASCC cachexia study group

Chief: Koichi Takayama, MD

Kyoto prefectural university of medicine

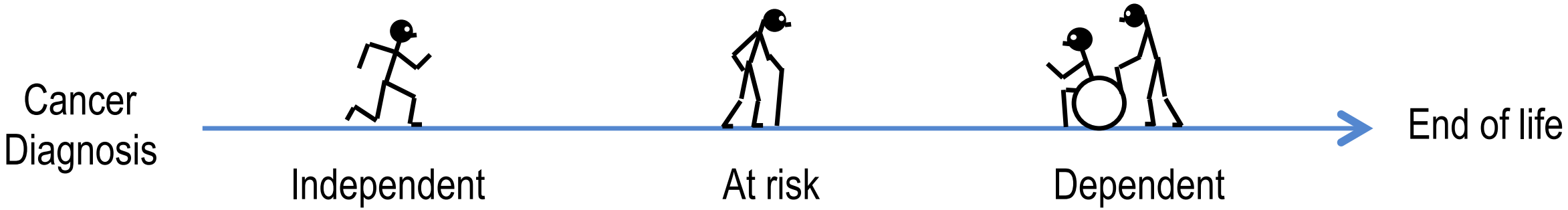
Support from the grant in aid for the Japan Agency for Medical Research and Development (AMED)

Core concepts of the NEXTAC

We aim to develop a new multimodal intervention specific for elderly cancer patients to prevent disability.

It was designed to …

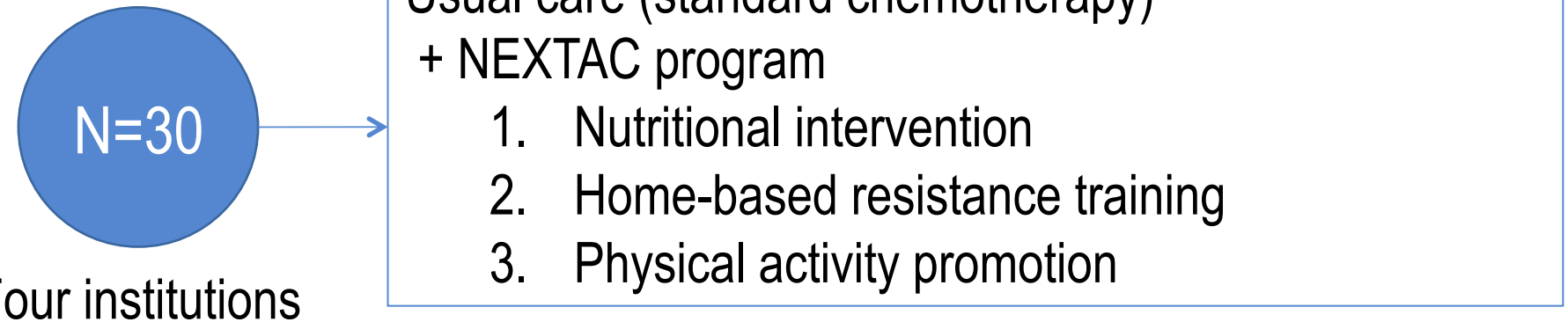
1. Be accepted not only by fit elderly but also frail elderly
2. Maximize compliance without reducing efficacy
3. Start as early as possible
4. Keep motivation and promote behavioral changes by education



The NEXTAC-ONE feasibility study

Patients:

Advanced NSCLC or Pancreatic cancer, being to start chemotherapy
ECOG-PS 0-1, ≥70 y.o., no disability (Barthel index ≥95 points)



Four institutions from Japan

6 sessions in 8 weeks

Endpoint

Primary: Feasibility (attendance, threshold 0.45, expectation 0.70)
Secondary: Safety, Compliance, Adherence

Trial registration No. UMIN000023207

1. Nutritional Intervention

Inner Power®
Otsuka Pharmaceutics

1) Nutritional advice
2) BCAA-rich supplements
3) Management of NIS (nutritional impact symptoms)
   e.g. mucositis, taste disturbance, and anorexia

BCAA: branched-chain amino acid

2. Home-based resistance training

Level	Prescription
1	Sit and stand up + Calf raises + Knee extensor
2	Level 1 + Hip flexion + Hip Abductor
3	Level 2 + Strap 1kg weight on ankle

Sit and stand up

Calf raises

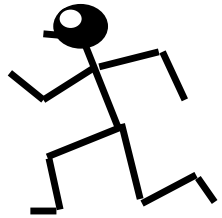
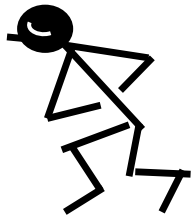
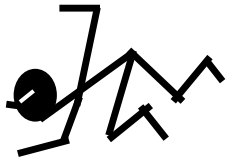
Hip flexion

±

Knee extensor

Hip Abductor

3. Physical activity Promotion

	4 steps	Examples
	Goal setting & Feedback	• Set step goal: baseline + 2000 steps • Self-monitoring: taking diary
	Action planning	• Regular walking & House chores • Stay in the job
	Active management of symptoms	• Cosmetic problems (e.g. Skin rash) • Physical problems (e.g. Diarrhea)
	Fall prevention	• Do not use sandals or slippery shoes • Maintain a clutter-free floor

Mouri T & Naito T, Asia Pac J Oncol Nurs, 2018 [E-pub ahead of print]

Patient characteristics

Variables	N = 30
Median age (range)	75 (70-84)
Women:Men	10:20
ECOG-PS	n (%)
0	11 (37)
1	19 (63)
Lung cancer	24 (80)
Pancreatic cancer	6 (20)
Stage IV	27 (90)
Chemotherapy	
Cytotoxic	20 (67)
Targeted	10 (33)
Lifestyle, n (%)	
Unemployed	18 (60)
No exercise habit	16 (53)
Living alone	4 (13)
Nutritional status	
Cancer cachexia	12 (40)
Skeletal muscle depletion	21 (70)

Feasibility was defined as attendance

Sessions	Proportion
Nutritional sessions	98%
Exercise sessions	97%
Total attendance ratio (95% CI) % of patients who attended ≥ 2/3 sessions	97% (83-99)

Statistical design
Expected proportion: 70%
Threshold proportion: 45%

This study met the primary endpoint and the NEXTAC is feasible.

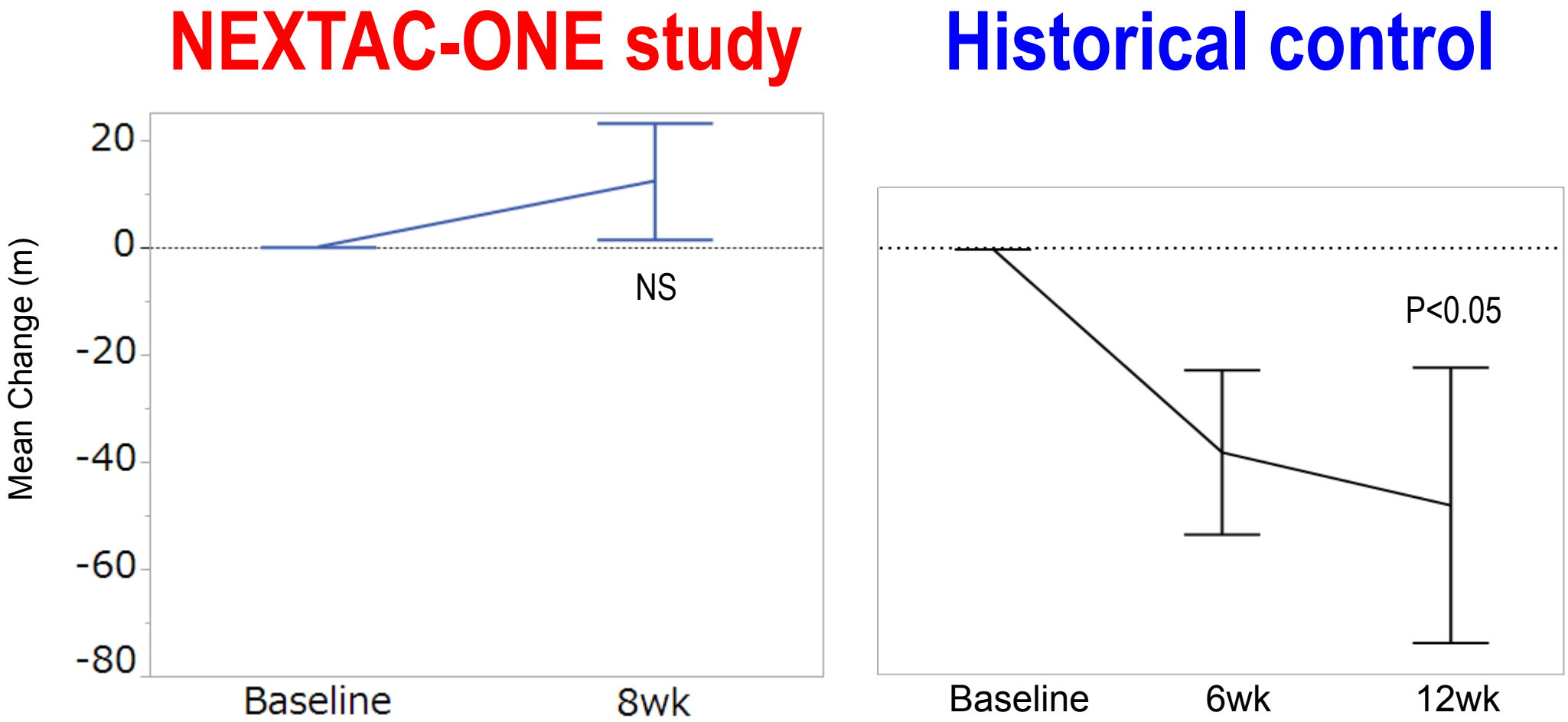
Compliance

Number of patients	29
Nutrition	Median % (IQR)
Diet diary fill-in day	90 (14-98)
Supplement consumption day	99 (88-100)
Daily resistance training	
Exercise diary fill-in day	94 (51-98)
Performance day	91 (69-95)
Physical activity	
Pedometer wear day (≥5 h/day)	98 (85-100)

Adherence

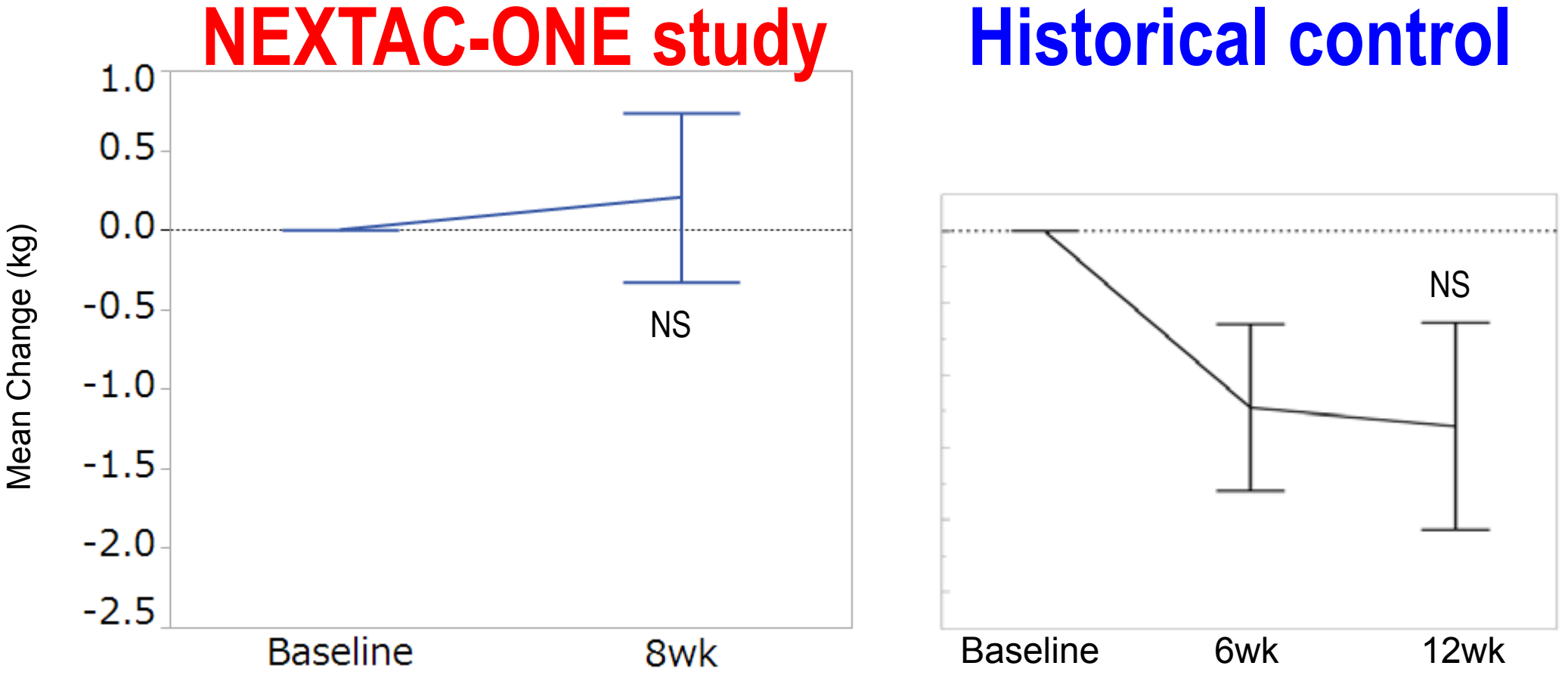
Period	First month N (%)	Second months N (%)
Number of patients	29	29
Nutrition		
Adequate caloric intake	25 (89)	25 (86)
Adequate protein intake	24 (83)	24 (83)
Physical activity		
Indoor activity ↑ or →	25 (86)	23 (79)
Outdoor activity ↑ or →	20 (69)	20 (69)
Daily steps ↑	20 (69)	13 (45)

Change in 6-minute walk distance



Naito T, BMC Cancer 2017

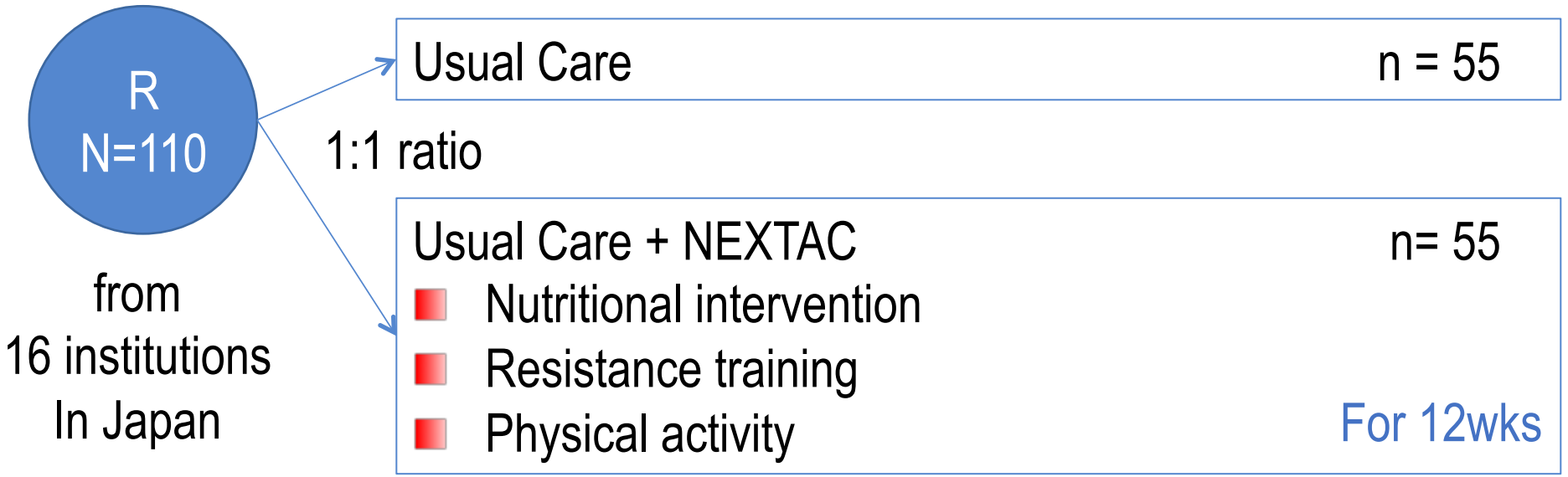
Change in Hand-grip strength



Naito T, BMC Cancer 2017

The NEXTAC-TWO study, a randomized P2 study

Patients: Advanced NSCLC or Pancreatic cancer, ECOG-PS 0-2



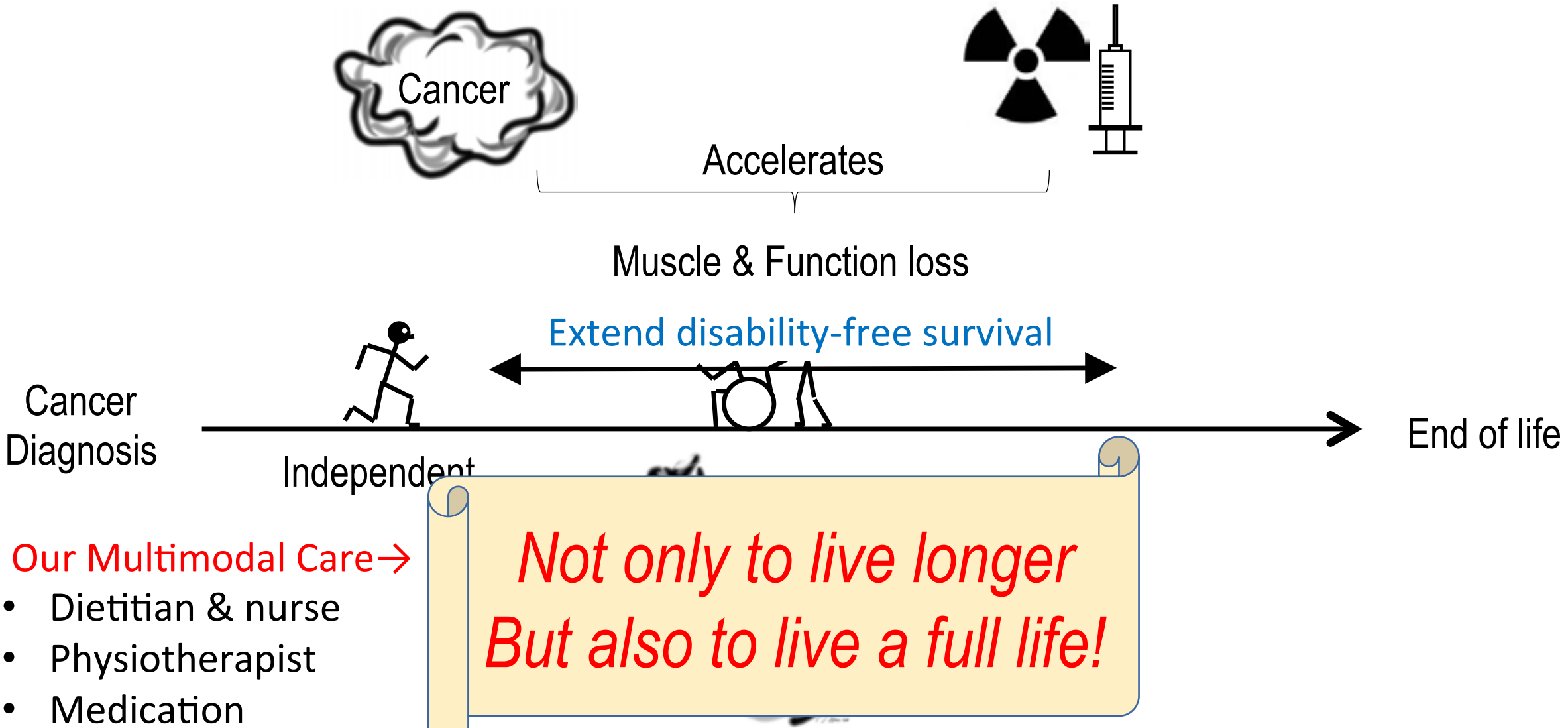
Primary Endpoint

Disability-free survival

Definition: Time until development of disability (modified KATZ index)

Trial registration No. UMIN000028801

Future Image of Cachexia Care



Our Multimodal Care→

- Dietitian & nurse
- Physiotherapist
- Medication

Not only to live longer
But also to live a full life!

Thank you for attention !

Acknowledgement

- *Shizuoka Cancer Center*

  Taro Okayama PT, Takashi Aoyama RD, Toshimi Inano RD, Ayumu Morikawa RN, Miwa Sugiyama RN, Keita Mori PhD, Akira Tanuma MD, Toshiaki Takahashi MD, Ms. Kanae Sasaga, Ms.Yukino Nagai

- *Kyoto university*, Katsuhiro Omae PhD

- *JASCC & JASCC cachexia study group*

  Koichi Takayama MD, Takashi Higashiguchi MD, Akio Inui MD, Tetsuya Tsuji MD, Teiko Yamaguchi RD, Takako Mouri RN, Hideki Aragane MD, Shuichi Mitsunaga MD, Noriatsu Tatematsu PT, Satoru Miura MD, Florian Strasser MD, Kazuo Tamura MD