Faculty Disclosure

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Honoraria/Expenses</th>
<th>Consulting/Advisory Board</th>
<th>Funded Research</th>
<th>Royalties/Patent</th>
<th>Stock Options</th>
<th>Ownership/Equity Position</th>
<th>Employee</th>
<th>Other (please specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ono pharmaceutics</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
73 y.o. man with advanced lung cancer & bone mets

Assessment
- Muscularity index 42 cm²/m² → Muscle depletion
- Weight loss (6mo) - 4.5% → Cancer cachexia

Cancer treatment
Palliative bone radiation & chemotherapy

Body composition in advanced cancer patients

Lumbar CT at the time of diagnosis
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**
“κακός ἔξις”, Cachaxia

Hippocrates
460 BC – 370 BC

**Ancient China**
“萎病”: Atrophic illness

Yellow emperor
2000 BC

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

“Kokonhoi”, Tsugen Koga, 1692
National Institute of Japanese Literature
“Cachexia” was imported to Japan in 18th century, the late Edo period

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

Utagawa Genzui (1756-1798)

Genzui’s translation draft “Ushi Hikyu”, 1793
National Diet Library, Japan
And today, Cachexia was not yet overcome.

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

After >2000 years, we still suffer from cachexia

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

Bruera E BMJ 1997, p1219

2. Takayama K, Support Care Cancer (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
Number of patients living with advanced cancer & cachexia are increasing in JAPAN

- NSCLC: 49% Non-cachexia, 54% Cachexia
- Colorectum: 64% Non-cachexia, 36% Cachexia
- Gastric: 78% Non-cachexia, 22% Cachexia
- Pancreas: 70% Non-cachexia, 30% Cachexia
- Biliary tract: 63% Non-cachexia, 37% Cachexia
- HCC: 64% Non-cachexia, 36% Cachexia
- Bladder: 64% Non-cachexia, 36% Cachexia
- Esophageal: 62% Non-cachexia, 38% Cachexia

Web-based survey in 2016, Copyright© 2018 IQVIA. Reprinted with permission
Physicians’ Awareness of the diagnostic criteria of Cachexia in JAPAN

36% Aware
64% Unaware

2016 survey in Japan

Web-based survey in 2016, Copyright© 2018 IQVIA. Reprinted with permission
Today’s Agenda

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

What is the true goal of cancer cachexia?
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

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

83%
Longitudinal changes in physical parameters within 6-12 weeks from initiation of chemotherapy.

Naito T, BMC Cancer, 2017
MSCC 2015 Miami
Measuring functional prognosis

Disabling event: Losing 10 points of Barthel index

Cancer Diagnosis → Disability-free survival → With disability → Death

One person’s survival time
Cachectic patients easily develop disability

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

Frequent disabling events:
1. Stair climbing
2. Moving
3. Bathing
4. Toilet use

Cachexia (N=19)  Non-cachexia (N=11)

Naito T, BMC Cancer, 2017
MSCC 2016 @Copenhagen
Today’s Agenda

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

Cachexia is a multifactorial disease
Pre-MENAC study

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual care</td>
<td>n=21</td>
</tr>
<tr>
<td>Usual care + MENAC</td>
<td>n=25</td>
</tr>
</tbody>
</table>

1:1 ratio

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

6 weeks

3 institutions from Norway and UK

Number of interventions increases

<table>
<thead>
<tr>
<th>Combinations</th>
<th>Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single intervention</td>
<td>76% in NSAIDS</td>
</tr>
<tr>
<td></td>
<td>60% in Exercise</td>
</tr>
<tr>
<td></td>
<td>48% in Supplements</td>
</tr>
<tr>
<td>2 combinations</td>
<td>20 – 48%</td>
</tr>
<tr>
<td>3 combinations</td>
<td>12%</td>
</tr>
</tbody>
</table>

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)

N=30
Four institutions from Japan

Usual care (standard chemotherapy) + NEXTAC program
1. Nutritional intervention
2. Home-based resistance training
3. Physical activity promotion

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

Trial registration No. UMIN000023207
1. Nutritional Intervention

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

<table>
<thead>
<tr>
<th>Level</th>
<th>Prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sit and stand up + Calf raises + Knee extensor</td>
</tr>
<tr>
<td>2</td>
<td>Level 1  + Hip flexion + Hip Abductor</td>
</tr>
<tr>
<td>3</td>
<td>Level 2  + Strap 1kg weight on ankle</td>
</tr>
</tbody>
</table>

![Sequence of exercises](image)
## 3. Physical activity Promotion

<table>
<thead>
<tr>
<th>4 steps</th>
<th>Examples</th>
</tr>
</thead>
</table>
| **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

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

<table>
<thead>
<tr>
<th>Sessions</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional sessions</td>
<td>98%</td>
</tr>
<tr>
<td>Exercise sessions</td>
<td>97%</td>
</tr>
<tr>
<td>Total attendance ratio (95% CI)</td>
<td>97% (83-99)</td>
</tr>
<tr>
<td>% of patients who attended ≥ 2/3 sessions</td>
<td></td>
</tr>
</tbody>
</table>

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

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

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>29</td>
</tr>
<tr>
<td><strong>Nutrition</strong></td>
<td></td>
</tr>
<tr>
<td>Diet diary fill-in day</td>
<td>90 (14-98)</td>
</tr>
<tr>
<td>Supplement consumption day</td>
<td>99 (88-100)</td>
</tr>
<tr>
<td><strong>Daily resistance training</strong></td>
<td></td>
</tr>
<tr>
<td>Exercise diary fill-in day</td>
<td>94 (51-98)</td>
</tr>
<tr>
<td>Performance day</td>
<td>91 (69-95)</td>
</tr>
<tr>
<td><strong>Physical activity</strong></td>
<td></td>
</tr>
<tr>
<td>Pedometer wear day (≥5 h/day)</td>
<td>98 (85-100)</td>
</tr>
</tbody>
</table>
## Adherence

<table>
<thead>
<tr>
<th>Period</th>
<th>First month</th>
<th>Second months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td><strong>Nutrition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate caloric intake</td>
<td>25 (89)</td>
<td>25 (86)</td>
</tr>
<tr>
<td>Adequate protein intake</td>
<td>24 (83)</td>
<td>24 (83)</td>
</tr>
<tr>
<td><strong>Physical activity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indoor activity ↑ or →</td>
<td>25 (86)</td>
<td>23 (79)</td>
</tr>
<tr>
<td>Outdoor activity ↑ or →</td>
<td>20 (69)</td>
<td>20 (69)</td>
</tr>
<tr>
<td>Daily steps ↑</td>
<td>20 (69)</td>
<td>13 (45)</td>
</tr>
</tbody>
</table>
Change in 6-minute walk distance

NEXTAC-ONE study

Historical control

Naito T, BMC Cancer 2017
Change in Hand-grip strength

NEXTAC-ONE study

Historical control

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)*

**R N=110**

1:1 ratio

- Usual Care  
  n = 55

- Usual Care + NEXTAC  
  n= 55
  - Nutritional intervention
  - Resistance training
  - Physical activity

For 12wks

from 16 institutions
In Japan

Trial registration No. UMIN000028801
Future Image of Cachexia Care

Accelerates

Muscle & Function loss

Cancer

Extend disability-free survival

Cancer Diagnosis

Independent

End of life

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

Our Multimodal Care→
• Dietitian & nurse
• Physiotherapist
• Medication
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