WHO Definition Palliative Care - 2002

“Palliative care is an approach which improves the quality of life of patients facing the problems associated with life-threatening illness, through prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.”
Binary Views
Oncology

Anatomy Rules All!
Symptoms? Handmaidens

Adopt concept
Biology (Symptoms) key as anatomy

Suffering
Tumour Progress
Factors driving tumor and symptoms

- Chronic Inflammation
- Chronic Stress

Reinforcement ... Common Endpoints
Advancing Cancers

Infiltrating → TAM → TIL

Growth Factors ↓ Tumour Immunity
Angiogenesis Th2 ↑ Th1 ↓
Proteases – matrix

We suggest that the inflammatory cells and cytokines found in tumours are more likely to contribute to tumour growth, progression and immunosuppression than they are to mount an effective host anti-tumour response... some types of inflammation may provide ‘the fuel that feeds the flames’.

**CHRONIC INFLAMMATION**

- **LIVER**
  - ↑AFP (note CRP)
  - ↓drug metabolism

- **MUSCLE**
  - ↓synthesis
  - ↑proteolysis

- **HYPOTHALAMUS**
  - ↓appetite
  - ↑sympathetic activity
  - ↑REE
  - ↑cortisol
  - ↓testosterone

- **BRAIN**
  - depression

- **FAT**
  - ↑lipolysis
  - ↓lipoprotein lipase

- **GUT**
  - early satiety
### Median survival by CRP Trajectory

<table>
<thead>
<tr>
<th>CRP Trajectory</th>
<th>Median survival (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal ⇒ Normal</td>
<td>21.6</td>
<td>11.9-31.6</td>
</tr>
<tr>
<td>Normal ⇒ Abnormal</td>
<td>12.3</td>
<td>6.5-18.1</td>
</tr>
<tr>
<td>Abnormal ⇒ Normal</td>
<td>10.7</td>
<td>7.6-13.5</td>
</tr>
<tr>
<td>Abnormal ⇒ Abnormal</td>
<td>8.3</td>
<td>7.0-9.5</td>
</tr>
</tbody>
</table>

Log Rank (Mantel-Cox)<0.001

JCO suppl. 2009 abstract 8092
Correlation Between CRP and Severity of Symptoms Reported by Patients

![Graph showing the correlation between C-Reactive Protein (CRP) levels and mean score on ESAS (EORTC Investigator-Generated Symptom Assessment Scale) for various symptoms: Strength, Appetite, SOB, Daytime Sleepiness, Nervousness, Constipation, Depression, Others, Nausea, and Vomiting. The graph compares CRP levels of 0-9 g/L to ≥10 g/L in terms of symptom severity.](image-url)
STRESS

HPA
Cortisol

Autonomic tone
Norepinephrine

Metastatic Risk
Tumor Growth
Inflammatory Factors

(Modelled on Lutgendorf et al, JCO - 2010; 28-4094)
Stress

Basic data

Cytokines
Tumor cell lines
Human melanoma

Survival
Mouse tumor models
Post surgery
Etodolac and Propranolol

Human Ovarian nude mice

Propranolol

Switch from Th1 to Th2 immune response

Yang et al.

Ben Eliyahu

Lee et al.

Reiche et al.
Stress – human correlation

Breast cancer.................................Spiegel Anderson
GI cancer............................................Kuchler
Melanoma.............................................Fawzy

Programs
Cognitive/Behavioural
Mindfulness
Supportive
Exercise – Yoga

Correlations with immuno endocrine change

Biobehavioral influences on cancer progression
## Palliative Care Success

<table>
<thead>
<tr>
<th>GOOD</th>
<th>MEDIUM</th>
<th>NOT SO GOOD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>Dyspnea</td>
<td>Delirium</td>
</tr>
<tr>
<td>Social Support</td>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>Quality of Life</td>
<td></td>
<td>Anorexia Cachexia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Function</td>
</tr>
</tbody>
</table>
Figure 3. Kaplan–Meier Estimates of Survival According to Study Group.

Palliative Care – The Fourth Phase of Cancer Prevention

MacDonald N
Cancer Prevention and Detection 1991 15(3) ;251
A Palliative Rehabilitation Program Improves Patient Functioning

Dr. Neil MacDonald

Palliative Rehabilitation Program, Bruyère Continuing Care; University of Ottawa, Ottawa, Canada
Methods

• Participants
  • Patients with advanced cancer, completed anticancer treatment
  • Adults who are 18 years of age and older
  • Ability to participate in a nutritional and/or physical program
  • Experiencing symptoms of anorexia, fatigue, weakness, malnutrition, pain and/or depression
  • Palliative performance score of 50% or above
PHYSICIAN ONCOLOGISTS
Medical Intervention

PHYSIOTHERAPIST
Functional Evaluation and Rehabilitation

PATIENT AND FAMILY

DIETITIAN
Nutritional Evaluation and Recommendations

NURSING, PSYCHOLOGIST, OCCUPATIONAL THERAPIST, SOCIAL WORKER

Slide courtesy Nelda Swinton
Methods

• Procedure
  • Initial assessment (T1) using measures listed below
    • 8-week program
    • Physiotherapy: 2x/week;
    • Medical intervention as needed (physician, nurse);
    • Optional additional interventions (social work, dietetics, occupational therapy)
  • Completion assessment (T2) measures below re-administered
  • Three-month follow-up (T3) measures below re-administered
Methods

Measures included:

- CRP serum level
- Eastern Cooperative Oncology Group (ECOG)
- Edmonton Symptom Assessment Scale (ESAS),
- Patient Generated Subjective Global Assessment (PG-SGA),
- MD Anderson Symptom Inventory (MDASI),
- Multidimensional Fatigue Inventory (MFI),
- Berg Balance test,
- 6 minute walk test (6MWT),
- Reach Forward,
- Timed-up-Go (TUG),
- Grip strength
## Results - Participants

<table>
<thead>
<tr>
<th>Program Referrals</th>
<th>N=284</th>
</tr>
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<tbody>
<tr>
<td>Did not start</td>
<td>37</td>
</tr>
<tr>
<td>Did not complete</td>
<td>92</td>
</tr>
<tr>
<td>Completed</td>
<td>155</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>I or II</td>
<td>23</td>
<td>14.8%</td>
</tr>
<tr>
<td>Stage III</td>
<td>47</td>
<td>30.3%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>85</td>
<td>54.8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Discharge Reason</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Progressation</td>
<td>51</td>
</tr>
<tr>
<td>Personal/Unknown</td>
<td>35</td>
</tr>
<tr>
<td>Deceased</td>
<td>2</td>
</tr>
<tr>
<td>Geographically Inaccessible</td>
<td>2</td>
</tr>
<tr>
<td>Active treatment</td>
<td>1</td>
</tr>
<tr>
<td>Too well to participate</td>
<td>1</td>
</tr>
</tbody>
</table>

Total N = 132
Interference of Symptoms
MD Anderson Symptom Inventory (MDASI)

January – December 2010

General Activity
Mood
Work
Relationships
Walking
Enjoyment

- General Activity: p<0.001, d=0.6
- Mood: p<0.001, d=0.44
- Work: p<0.001, d=0.47
- Relationships: p=0.001, d=0.33
- Walking: p<0.001, d=0.40
- Enjoyment: p<0.001, d=0.45
Symptom Burden
Edmonton Symptom Assessment scale (ESAS)

*Only significant p-values are reported*
Malnutrition
Patient-Generated Subjective Global Assessment

PGSGA

T1

T2

p<0.001
d=0.39

*Only significant p-values are reported
**Longitudinal Results**

**MD Anderson Symptom Interference**

- General Activity: 0.48
- Mood: 0.10
- Work: 0.09
- Relationships: 0.07
- Walking: 0.04

- Enjoyment: $p=0.23$, 0.29

*Only significant p-values are reported*
Mean Edmonton Symptom Assessment System (total symptom distress score [TSDS]) and Palliative Performance Scale (PPS) score.

Values below data points represent the total number of complete assessments available at a given week. Bars represent 95% CIs for the respective mean scores.

If true the importance to cancer patients is major and must lead to prioritizing integrated palliative care/chemo-bio trials.

A substantive change in both oncology thinking and trial structure is required. We must study whole care packages not simply drugs.
MENAC Trial - EAPC Research Network

Stratify advanced lung, pancreas, colorectal

Standard Palliative Care

Nutrition – counseling – HMB&EPA
Exercise
Drug - Celecoxib

Stratify – Weight Loss – CRP - Chemotherapy

Courtesy Stein Kaasa
PHYSICIAN ONCOLOGISTS
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Nutritional Evaluation and Recommendations

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Slide courtesy Nelda Swinton
Social Support

1. Childhood – ‘Mark of Cain’
   Early stress – lifetime
   risk – chronic
   inflammation

2. Cancer Risk

3. Response – poor

4. Symptoms accentuated – psychosocial
   others?

5. ↑ CIS
   ↑ Sympathetic drive
The Glorious Future

WHEN

• Symptom care is married with other anti-chronic illness approaches from time of diagnosis
• Access to nutrition – rehabilitation strengthen and maintain function and control fatigue are an integral part of palliative care
• A change in research and educational priorities reflects the above changes in the care of chronic illness
• A commitment to interdisciplinary collaboration to optimize patient outcomes is the norm
When the primacy of chronic inflammation and stress are recognized and this knowledge is uniformly used to stage and direct cancer therapy

A closer meld between 1st World medicine and 3rd World medicine
The Glorious Future

Research

1. Studies include economic impact
2. Yes, a Palliative Care Research Network - but one integrated with other Oncology trials
The Glorious Future

When football players are wearing plaid
Results - Illness Status

**CRP**

- T1: d=0.2
- T2: d=0.2

**ECOG PS**

- T1: p<0.001*
- T2: d=0.42

*Only significant p-values are reported*
Stress – human correlation

Childhood stress - chronic disease risk
Social deprivation – ovarian cancer (Lutgendorf) _ colorectal cancer (McMillan)
Correlation with immune neuroendocrine change

“Collective evidence points to a prominent role for chronic stress in cancer growth and metastasis”

Moreno-Smith M. et al Impact of stress on cancer metastasis.
Future Oncology Dec2010
Improving Symptom Research

1. Change in mind set. Symptoms reflect tumour activity and are as important as partial anatomic change in tumour mass.

2. Change trial priority.
   - Curative trials
   - Pragmatic trials – care package
   - Fastidious trials – limited studies on drugs with limited inclusion/exclusion clauses
   - ‘Me too’ trials
Stress

Mechanisms:
cancer initiation
tumor growth
angiogenesis
metastases
reduce apoptosis
reduce $\text{TH}_1$ AND lymphocytes

Armaiz-Pena et al
Brain behavior and immunity 2009; 23:10-15
Inflammation

Immuno-neuroendocrine aberrations

1. ↑ CRF – cortisol
2. ↑ sympathetic activity
   - ↑ Cytokine activity
   - ↑ Pulse – REE
   - ↑ Psychosocial stress
3. ↓ testosterone
   - Hypogonadism
     - sex drive
     - activity
**Physical Measures**

- **Berg:**
  - T1: p=0.001, d=0.14
  - T2: p<0.001, d=0.49

- **Reach Forward:**
  - T1: p<0.001, d=0.50
  - T2: p<0.001, d=0.31

- **Timed up-and-go:**
  - T1: p<0.001, d=0.10

- **Grip Strength:**
  - T1: p<0.001, d=0.31

*Only significant p-values are reported.*

**Six-minute Walk Test:**

- T1: p<0.001, d=0.31
Acute Inflammation

• Innate Immune System
  – Wound healing
  – Tissue repair
  – Angiogenesis

• Adaptive Immune System
  – Specific response to antigen
  – Cytotoxic T cells
Chronic Inflammation

• Innate
  
  Promote tumour growth and spread

• Adaptive
  
  Reduced NK cell activity
Cancer Cachexia - Anorexia
Activation of microglial cytokines → CNS → Hypothalamus → MC4 → anorexia

Circulating cytokines → Balance Vagal Input

Sympathetic tone REE Norepinephrine → MC4 → CNS Hypothalamus
Chronic Inflammation - Cancer

- Immune response often facilitates tumor progress
- Tumor cells produce inflammatory chemical mediators assisting growth
- Inflammatory mediators enhance many cancer symptoms
- Early evidence – anti-inflammatory agents may modify the course of cancer
- Will anti-inflammatory (palliative) therapies improve life quality and quantity?
- Relief of cachexia - survival?
Palliative Care-improve outcomes?

• Quality of life  ---  Seven studies
  – Yes  – 5/7

• Symptoms  ---  Fifteen studies
  – “overall the results of these 15 studies provide little evidence to support the efficacy of palliative care interventions in alleviating physical symptoms” –

Palliative Care – what we do

1. Identify – manage psychosocial issues
2. Emphasis on caregiver support
3. Relief of physical causes of suffering
4. Focus on Nutrition
5. Focus on muscle function and rehabilitation
Changes in ESAS Scores after 8-week CNR program for Patients with Advanced Cancer presenting with CRP < 12 at Initial CNR Evaluation (N = 95)

Note: Higher scores indicate worse symptoms

* p < 0.05 vs. Initial
Initial and Final Total ESAS Scores for Patients with Advanced Cancer presenting with CRP < 12 or CRP ≥ 12 at Initial CNR Evaluation (N = 103)

**Note:** Higher scores indicate worse symptoms

* *p < 0.05 vs. Initial*
Percentage of Patients with Advanced Cancer who Lost, Maintained or Gained Weight during the CNR program by Inflammatory Status (N = 114)

\[ p = 0.01 \]
Initial and Final ESAS Anorexia Scores for Patients with Advanced Cancer presenting with CRP < 12 or CRP ≥ 12 at Initial CNR Evaluations (N = 117)

Note: Higher scores indicate worse symptoms

* p < 0.05 vs. Initial
Percentage of Patients with Advanced Cancer with Taste &/or Smell Alterations at Initial and Final CNR Evaluations (N = 103)

* $p < 0.05$ vs. Initial; † $p < 0.05$ vs. CRP < 12
Evaluation

• High patient satisfaction
• Advanced cancer patients can exercise
• CRP status determines completion of an exercise program
• Measured improvements in appetite, weight and function
Multimodal program

Is our program anti-inflammatory?

1. Dietary advice – yes
2. Exercise – yes
3. Psychosocial component – yes
4. Drugs – not really

Note – no overall change in CRP status
Stress

Animal Data

• Riley.................................................. Tumor Growth
• Sloan et al........................................... Metastases

Chronic stress mouse model

30 x ↑ metastases

Blocked by propranolol

Sloan et al. CancerRes2010;70:1042
1. Identify – manage psychosocial issues
2. Emphasis on caregiver support
3. Relief of physical causes of suffering
4. Focus on Nutrition
5. Focus on muscle function and rehabilitation
What We Must Do

Add focus on Muscle Support and Patient Function
Add focus on Nutrition
Hypothesis – Palliative Care interventions may impact on patient survival as well as Q/L.

Animal data is sufficient to support this hypothesis. Human data is very modest but compelling.
Propranolol - Atenolol

• Effects on $\beta$ adrenergic blockade

Breast cancer
