Clinical Management of cachexia and fatigue - physical activity interventions

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Background

- Pioneers in physical exercise and oncology
- First studies in late 1980s
- 10 weeks interval based aerobic training among breast cancer patients
- Functional capacity ↑, body composition ↑, nausea ↓
- Feasible and acceptable
- Significant effects on the selected outcomes

MacVicar MG et al., 1989; Winningham ML et al., 1988, 1989
Physical exercise and cancer
Prior research - what do we know?

• Several excellent systematic reviews and metanalysis

• General exercise prescriptions guidelines
  – Supervised or home-based
  – Moderate intensity (50-75 % of baseline maximal heart rate of aerobic capacity)
  – 3 sessions per week/10-60 minutes per session and 12-15 weeks
  – Aerobic or resistance exercise, combination of aerobic and resistance exercise

Fong et al., BMJ, 2012; Craft et al., Cancer Epidemiol Biomarkers Prev, 2012; McNeely et al., CMAJ, 2006; Knols et al., JCO, 2005; Jones et al., Lancet Oncol 2006; Speck et al., J Cancer Surviv, 2010; Cramp et al., Cochrane update, 2012
Physical exercise and cancer
Prior research - what do we know?

• Speck et al., 2010 identified 66 high-quality studies
  – Examined 60 different physiological, functional, biological or psycho-social outcomes

• During or after treatment
  – 60 % after treatment, 40 % during

• Majority breast cancer patients
  – Fewer studies including NSCLC, hematological malignancies and various types of cancer populations, none palliative populations

• Very few adverse events reported
Physical exercise and cancer
Prior research - what do we know?

• Significant improvement in:
  – Muscular strength $\uparrow$
  – Aerobic capacity $\uparrow$
  – Functional QoL $\uparrow$
  – Fatigue $\downarrow$
  – Anxiety $\downarrow$
  – Self-esteem $\uparrow$

Fong et al., BMJ, 2012; Craft et al., Cancer Epidemio Biomarkers Prev, 2012; McNeely et al., CMAJ, 2006; Knols et al., JCO, 2005; Jones et al., Lancet Oncol 2006; Speck et al., J Cancer Surviv, 2010; Cramp et al., Cochrane update, 2012
Physical exercise and cancer
Prior research - what do we know?

• Few studies concerning patients with advanced stage of disease (Lowe, 2009; Maddocks, 2009)
  – Small number of RCT’s – advanced cancer/palliative patients (Oldervoll et al., 2011; Headly et al., 2004)
  – Several prospective pre-post interventions (Lowe et al. 2013, Oldervoll et al. 2006; Porock, 2000; Crevenna; 2003)

• No published RCT’s including patients suffering from cachexia
Cancer cachexia

- "A multifactorial condition characterised by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment»
  
  Fearon et al., Lancet Oncol, 2011

- 60 – 80 % might develop cachexia among patients with advanced cancer

- Prevalence is depending on cancer type
Cancer Cachexia

- No consensus how to treat
- Need to treat early in the trajectory of cachexia

**Muscle loss**

- Loss of skeletal muscle mass
  - a key clinical feature of cachexia
  - an important side-effect of systemic cancer treatment

- Muscle loss is also related to reduced tolerance for chemotherapy, reduced treatment response and shorter survival

Awad S et al 2012; Marked changes in body composition following neoadjuvant chemotherapy for oesophagogastric cancer.
Why physical exercise (PE) in patients with cachexia?

• PE is in general the best method to maintain muscle mass

• It has capacity to counter-balance inactivity atrophy, decrease muscle catabolism and might reduce inflammation
Cancer cachexia

- Few effective therapeutic options
- Lack of success of unimodal treatment
- Include patients in an early phase
- RCT’s
- Multimodal treatment is necessary
  - Physical exercise
  - Nutrition (both nutritional supplements and advice)
  - Anti-inflammatory treatment with NSAID

Solheim and Laird, Opin Support Palliat Care, 2012
Advanced cancer – PE and effects on muscle strength and mass?

- **Systematic review** (Stene et al., resubmitted Crit Rev Oncology 2013)

- Primarily, the idea for this review was to examine the scientific evidence of the effect of physical exercise on muscle mass and strength in cancer patients in a precachectic or cachectic stage

- By January 2012 no randomised controlled studies were identified
Trials included in the review

• Evaluate the scientific evidence of effect of physical exercise on muscle mass and strength in patients with cancer

• Only RCT’s

• Trials examining efficacy of physical exercise
  – muscle mass (lean body mass, fat free mass, cross-sectional area)
  – Muscle strength
Results – conclusions and future research

• 16 RCT’s included
• Aerobic (AE), resistance (RE) and combination of AE and RE
• Summary of results
  – **Muscle strength (n = 14 studies) –** exercise more effective than usual care (large effects)
  – **Muscle mass (n = 6 studies) –** show a tendency of better maintenance than usual care (small effects)
  – Possible RE more effective than AE both on muscle mass and strength? (Stene et al., 2013, submitted)
Results – conclusions and future research

• Most trials in patients with early stage cancer

• Only one trial among patients with advanced disease

• No studies including cachetic patients

• Rigorous exercise studies in patients with advanced cancer and at risk of cancer cachexia are warranted
Effects of PA on cachexia in non-cancer patients

• Cachectic patients with COPD (n = 10) and non-cachectic (n = 19)

• Intervention:
  – 45 min a day/3days each week for 10 weeks
  – High-intensity cycling training

• Results:
  – 6 minute walk and peak work rate increased similar in both groups
  – Quality of life improved only among non-cachectic patient

Vogiatzis et al., Eur Respi J 2010
Effects of PA on cachexia in non-cancer patients

- Mid-thigh cross-sectional area improved in both groups (less in cachexia patients)
- Both groups decreased type IIb fibres and increased muscle capillary/fibre ratio
Effects of PE on cachexia in tumour-bearing mice

• Effects of eicosapentiaenoic acid (EPA) and PE in cachectic tumour-bearing mice

• Intervention: Physical exercise combined with EPA

• Results:
  – Anti-inflammatory effect
  – Partial rescue of muscle mass and strength

  (Lira et al., Nutr Metab, 2011)
Physical exercise and cachexia

• Thus, even in presence of advanced disease and cachexia, muscle has the capacity to respond to physical exercise
Effect of PE on cancer related fatigue

• Physical activity beneficial to reduce cancer related fatigue during and after treatment

• Especially for those with solid tumours

• Further research is required to determine the optimal type, intensity and timing of an exercise intervention

(Cramp and Daniel, Cochrane 2008; Cramp and Byron-Daniel update 2012; McMillan EM, Newhouse I, J. Appl Physiol Nutr Metab. 2011)
PE – advanced cancer – effects on fatigue?

“Exercise interventions can lead to an improvement in fatigue in people with cancer, however, this beneficial effect is still to be proven for those in advanced stages of their illness”

(Payne, 2012, Interventions for fatigue and weight loss in adults with advanced progressive illness, Cochrane review)
Physical Exercise for Cancer Patients with Advanced Disease: A Randomized Controlled Trial

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a European Palliative Care Research Centre, Department of Cancer Research and Molecular Medicine, Faculty
Background - pilot

Oldervoll et al., Palliative and Supportive Care 2005; JPSM 2006; Lowe et al., Supportive Oncol., 2009
Results – RCT- Total fatigue (CCA)

No overall effect: (p = 0.12)

p = 0.002
p = 0.24
Results – Shuttle walk

Overall statistical and clinical significant effect in favor of the exercise group ($p = 0.008$)
Results - hand-grip strenght

Overall statistical and clinical significant effect in favor of exercise group (p = 0.01)
Results – bodyweight, drop outs and survival

• **Body weight**
  – Overall statistical and clinical significant effect in weight in favor of the exercise group

• **Drop outs**
  – Significantly higher drop out rate in the exercise group than in the control group (35 % vs 23 %)
  – Most frequent reason for withdrawal was *disease progression*
    • Deaths, did not adhere, dropped out before start

• **Survival**
  – No difference between the groups (16 and 17 months for those who completed)
  – Significantly lower survival in those who dropped out (5 months)
Conclusions

• Physical exercise may prevent physical deterioration in cancer patients with incurable disease
• Heterogenous population
• Future randomised studies should study the feasibility and effects of physical activity among patients suffering from cachexia at different stages
# Ongoing studies – physical exercise in advanced cancer

<table>
<thead>
<tr>
<th>ID (country)</th>
<th>Study characteris.</th>
<th>(N)</th>
<th>Setting</th>
<th>Intervention</th>
<th>Major outcomes</th>
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</thead>
<tbody>
<tr>
<td>NCT004057 82 (USA)</td>
<td>Stage IV (metastatic) breast cancer, 16 wk, 2 armed RCT</td>
<td>100</td>
<td>Home-based/supervised</td>
<td>Moderate intensity exercise vs waiting list</td>
<td>Physical functioning, PRO’s</td>
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<tr>
<td>NCT009854 00 (USA)</td>
<td>Stage IV or recurrent cancer; 16 WK; 2 armed RCT</td>
<td>150</td>
<td>Home-based</td>
<td>Combined endurance and resistance vs relaxation</td>
<td>Recruitment rate, feasibility, physical functioning, PRO’s</td>
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<tr>
<td>NCT01136083 (Taiwan)</td>
<td>Stage IV (inoperable) lung cancer; 16 wk; 2 arm RCT</td>
<td>60</td>
<td>Home-based/supervised</td>
<td>Aerobic exercise – 3 d/wk vs usual care</td>
<td>Aerobic capacity, PRO’s muscle function, body composition</td>
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<tr>
<td>NCT00869804 (Germany)</td>
<td>Stage IV (advanced) NSCLC single arm 8 wk</td>
<td>40</td>
<td>Supervised and home-based</td>
<td>5d/wk inpatients followed by 3 d/wk home-based</td>
<td>Feasibility, adherence, QOL, muscle strength</td>
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## Ongoing studies – advanced cancer – multimodal treatment

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<tr>
<td>NCT00625742 (USA)</td>
<td>Cancer patients with weight loss; single arm; 4 wk</td>
<td>40</td>
<td>Home-based</td>
<td>Aer. and resis. exercise + pharmacol intervention + nutritional supplement</td>
<td>Lean body mass</td>
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<tr>
<td>NCT00827164 (USA)</td>
<td>Stage I-IV head and neck undergoing adjuvant radiotherapy2 arm RCT; 12 wk</td>
<td>44</td>
<td>Supervised/home-based</td>
<td>Progressive resistance vs nutritional counseling</td>
<td>Feasibility, muscle strength, adherence, body composition fatigue, physical functioning</td>
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# Ongoing studies – advanced cancer – multimodal treatment

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</thead>
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<tr>
<td>NCT01540968 (Switzerland)</td>
<td>Metastatic NSCLC or gastrointest. (12 weeks, 2 armed RCT)</td>
<td>74</td>
<td>Not reported</td>
<td>progressive exercise training with nutritional supplement vs usual care</td>
<td>QOL</td>
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<tr>
<td>NCT01419145 (Norway)</td>
<td>Advanced NSLCL (stage III-IV) or pancreatic cancer</td>
<td>270</td>
<td>Homebased</td>
<td>RE and AE + nutrition and advice + anti-inflammatory medication</td>
<td>Muscle mass, Physical function (ActivPal + 6-minute walk test)</td>
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Summary

• Physical exercise (PE) improves physical performance, fatigue and functional quality of life in cancer patients

• Even in the presence of advanced disease, peripheral muscle has the capacity to respond to exercise and gain muscle mass

• However, further randomized trials are required including patients suffering from cancer cachexia
Summary

• PE should be offered early in the disease trajectory

• Include different types of PE at different intensities to improve compliance

• Multimodal approach is necessary including PE, nutrition and pharmacological treatment
Thank you for your attention