STEPPING OUT:
THE ROLE OF EXERCISE IN REHABILITATION POST HSCT

NEW STRATEGIES AND OUTCOMES

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38th Annual Meeting of the European Group for Blood and Marrow Transplantation
28th Meeting of the EBMT Nurses Group

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Outline

→ Background: Role of Ex-Reha in Cancer
→ Indication for Exercise in SCT
→ State of the Art: Exercise in SCT Patients
→ Result from new Studies
→ Conclusion and Future Directions
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Epidemiology → PA and Cancer Prevention

<table>
<thead>
<tr>
<th>Tumor</th>
<th>EVIDENCE-Classification: PA in Primary Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WHO (2002)</td>
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<tr>
<td>Colon</td>
<td>convincing</td>
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<tr>
<td>Breast</td>
<td>convincing</td>
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<tr>
<td>Prostate</td>
<td>possible</td>
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<tr>
<td>Endometrium</td>
<td>possible</td>
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<tr>
<td>Rectum</td>
<td>insufficient</td>
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<tr>
<td>Pancreas</td>
<td>insufficient</td>
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<tr>
<td>Lung</td>
<td>insufficient</td>
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<tr>
<td>Other tumor entities</td>
<td>insufficient</td>
</tr>
<tr>
<td>Colon</td>
<td>convincing</td>
</tr>
<tr>
<td>Breast</td>
<td>convincing (postmenopausal) limited convincing (premenop.)</td>
</tr>
<tr>
<td>Prostate</td>
<td>possible</td>
</tr>
<tr>
<td>Endometrium</td>
<td>possible</td>
</tr>
<tr>
<td>Rectum</td>
<td>- (tentative no)</td>
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<tr>
<td>Pancreas</td>
<td>limited convincing</td>
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<tr>
<td>Lung</td>
<td>limited convincing</td>
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<tr>
<td>Other tumor entities</td>
<td>No possible</td>
</tr>
</tbody>
</table>
Epidemiology → PA and Survival after Cancer

**Breast → 6 Studies:**
Risk reduction in cancer-specific mortality 34%; Reduced overall mortality after BC therapy 41%

Ibrahim & Al-Homaidh 2010 (Med Oncol)

**Colon → 4 Studies:**
40-60% lowered risk of overall and cancer-specific mortality

Haydon et al. 2006 (Gut); Meyerhardt et al. 2006-2009 (JCO)

**Prostate → 1 Study:**
40-60% risk reduction in overall and cancer-specific mortality

Kenfield et al. 2011 (JCO)

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PubMed → Exercise and Cancer

- **SURVIVAL**
- **PHYSIOLOGICAL**
- **PSYCHOSOCIAL**
- **SAFETY**

Number of studies vs Year:
### Guidelines

**American College of Sports Medicine Roundtable on Exercise Guidelines for Cancer Survivors**

Schmitz et al. 2010 - MSSE

### Evidence → Exercise & Cancer

<table>
<thead>
<tr>
<th></th>
<th>Safety</th>
<th>Aerobic Fitness</th>
<th>Strength</th>
<th>Flex</th>
<th>Body comp</th>
<th>QoL</th>
<th>Fatigue</th>
<th>Other Psychosocial</th>
<th>Other</th>
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</thead>
<tbody>
<tr>
<td>Breast (during)</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>-</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>(anxiety)</td>
<td>-</td>
</tr>
<tr>
<td>Breast (post)</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>(depression)</td>
<td>(function)</td>
</tr>
<tr>
<td>Prostate</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>-</td>
<td>B</td>
<td>B</td>
<td>A</td>
<td>(pain)</td>
<td>(lymphedema)</td>
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<td>Loco</td>
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<td>Gyn</td>
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<td></td>
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<tr>
<td>Home (no HSCT)</td>
<td>-</td>
<td>A</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home (HSCT)</td>
<td>A</td>
<td>C</td>
<td>C</td>
<td>-</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A= many RCTs  
B= few RCTs  
C= non-RCTs, observational studies
Recommandation of the Expert Panel

1. Return to activities as soon as possible post surgery
2. Avoid inactivity
3. 150 minutes PA per week of moderate intensity

→ No specific Recommandations possible due to lacking informations on „received“ exercise dose!

Schmitz et al. 2010 - MSSE

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Indications for physical exercise in HSCT I

**Reduced physical performance status**

**Immediately before allo-HSCT** (White et al., 2005, Chest)
- 58% of all patients had a reduced *endurance capacity*
- 39% of all patients had a reduced *strength capacity*
- 80% of all patients had an impaired *ventilatory capacity*

**Immediately before allo-HSCT** (Morishita et al., 2011; SuppCareCancer)
- Significant reduced *hand grip* and *knee extensor strength*
- Significant reduced *6-Minute Walk Distance*
- Significant reduced *physical functioning* and *QoL*

→ comparable with own data

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**Psychophysical Constitution prior to allo-HSCT**

*(Endurance Performance – 6MWT)*

![](chart.png)

Psychophysical Constitution prior to allo-HSCT  
(Max. Isometric Force – Handheld Dynamometry)

Upper Extremities
***

Lower Extremities
***


Psychophysical Constitution prior to allo-HSCT  
(Quality of Life - EORTC)

EORTC QLQ C30

1Reference Values obtained from EORTC Manual, Scott et al. 2008
Indications for physical exercise in HSCT I

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Immediately before allo-HSCT (Morishita et al., 2011; SuppCareCancer)
- Significant reduced hand grip and knee extensor strength
- Significant reduced 6-Minute Walk Distance
- Significant reduced physical functioning and QoL

≈ comparable with own data

~ 2 year after allo-HSCT (Kovalszki et al., 2008; BMT)
- More than 70% had a reduced endurance/strength capacity
- 90% of all patients had an impaired ventilatory capacity

Indications for physical exercise in HSCT II

Late effects allo-HSCT

- Exercise-induced shortness of breath, weakness (Baker et al., 2010, Leukemia)
- Functional performance substantially lower (physical function and role function) (Mitchell et al., 2010, BMT)
- 70% Hypertension, 30% Diabetes after two years (Majhail et al., 2009, BMT)
- 49% metabolic syndrome after 3 years (Majhail et al., 2009, BMT)
- Osteoporosis, neurosensory impairments, tremor, health-related quality of life, fatigue, psychological distress (Baker et al., 2010, Leukemia; Andrykowski et al., 2005, JCO; Hjermstad et al., 2004, BMT)

⇒ All late effects: Highly Inactivity-associated
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Exercise Interventions in HSCT Patients I

To date: 23 published studies examining the effect of physical exercise in the context of HSCT

- 10 Studies in allo-HSCT, 7 in auto-HSCT, 6 mixed populations
- Often Feasibility-Studies (small sample sizes, mix of allo- and auto-HSCT)
- Different intervention strategies (aerobic vs. resistance training vs. mixed types exercise vs. multimodal strategies)
- Variety of outcomes and assessment methods
- Mostly setting specific intervention strategies (inpatient vs. outpatient)

→ overall: very heterogeneous designs & methods

(Wiskemann et al., 2008, BMT; Spence et al., 2010, Cancer Treat Rev; Wolin et al., 2011 Leukemia)
Exercise Interventions in HSCT Patients II

Reported Effects:

- Stabilization effect on physical performance during inpatient period
- Improvements after HSCT (endurance, muscle strength)
- Positive effects on psychosocial and physical variables
  → QoL (predominantly functional subscales)
  → Body composition (weight gain)
  → reduced intensity of side-effects (e.g. nausea, vomiting, diarrhea, pain, sleep-disturbances)
  → faster hemato-/immunological reconstitution

→ overall: very heterogeneous results
→ Need for larger RCTs to confirm reported effects

(Wiskemann et al., 2008, BMT; Spence et al., 2010, Cancer Treat Rev; Wolin et al., 2010; Leukemia)

Exercise Interventions in Pediatric HSCT Patients

To date: 3 (4) published studies examining the effect of physical exercise in the context of HSCT

- All feasibility-studies (small sample sizes)
- Intervention strategies (3-5x/week → ~ 90% Adherence)
  (combined endurance and resistance training → in-patient)

Results

- No adverse events & negative effects on immune recovery
- Impaired strength capacity (from -28% till -65%)
- Increased physical fitness, functional mobility & QoL
- Tentative effects on dendritic cells

(Wolin et al. 2011, Leukemia; Rosenhagen et al., 2011 Clin Pediatric; Hadamofsky et al. 2012, in prep.)
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Effects of a partly self-administered exercise program prior to, during and after allogeneic stem cell transplantation – a randomized controlled trial


Aim:
To evaluate the feasibility and efficacy of a partly self-administrated physical exercise intervention before, during and after allogeneic hematopoietic stem cell transplantation (HSCT)

Primary Outcome:
- Cancer-Related Fatigue (CRF)

Secondary Outcomes:
- Physical performance/fitness
- Quality of Life, Distress, Depression, Anxiety

Published in Blood 2011, 177: 2604-2613
Study Design

Decision for PBSC / BMT (Companion check)

Exercise 5x/week (resistance and endurance training (2/3x))

Admission to hospital

Exercise 5x/week (starting with endurance training (5x) add resistance training (2x))

Discharge from hospital

Exercise 5x/week (resistance and endurance training (2/3x))

Aftercare check (6-8 weeks)

Catamnesis (6 months)

Geneva, EBMT 2012
Wiskemann – HSCT and Exercise

Patient-Flow

Eligible patients approached (n=141)

Agreed to participate and randomization (allocation) performed (n=112)

- Baseline -

Exercise group

Control group

Excluded from analyses (n=0)

Excluded from analyses (n=0)

Missing G Data 2 at c, estimated by LOGCF

Missing G Data 3 at t, estimated by LOGCF

Figure 2. CONSORT diagram.
Days in Treatment & Ex-Adherence

Table 2. Days in treatment periods per group

<table>
<thead>
<tr>
<th></th>
<th>Outpatient before HSCT</th>
<th>Duration of hospitalization</th>
<th>Outpatient after HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>15 (5-90)</td>
<td>43 (22-120)</td>
<td>52 (40-83)</td>
</tr>
<tr>
<td>Exercise</td>
<td>21 (5-112)</td>
<td>45 (24-92)</td>
<td>49 (39-63)</td>
</tr>
<tr>
<td>*P</td>
<td>.12</td>
<td>.64</td>
<td>.08</td>
</tr>
</tbody>
</table>

Table 3. Adherence to exercise intervention

<table>
<thead>
<tr>
<th>Study period</th>
<th>Before, %</th>
<th>During, %</th>
<th>After, %</th>
<th>Mean, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence to protocol</td>
<td>87.5</td>
<td>83.0</td>
<td>91.3</td>
<td>87.3</td>
</tr>
<tr>
<td>Exercise recommendation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing documentation</td>
<td>23.0</td>
<td>23.9</td>
<td>15.7</td>
<td>21.2</td>
</tr>
</tbody>
</table>

Fatigue

(POMS – Fatigue/müde)

ANOVA (rep. measures):
Interaction (Gr*Time):
F= 3.485 [p= .024]

Social Contact Group:
28% Increase ↑
Exercise Group:
15 % Reduction ↓
⇒ Intervention period
Physical Fitness
(Endurance Performance: 6 Minute-Walk-Test)

ANOVA (rep. measures):
Interaction (Gr*Time):
F = 3.846 [p = .018]

No significant differences in heart rate and Borg-Scale values at the end of 6MWT.

Physical Fitness
(Isometric Strength Performance: Handheld Dynamometry)

Note:
Greatest intervention effect for lower extremities
Main Results

• significantly improvement in fatigue scores
  (15% improvement in Exercise vs. 28% deterioration in Control group; p-values <0.01-0.03)

• significantly improvement in physical fitness and functioning scores
  (endurance and strenght performance; p-values 0.02-0.03)

• significantly reduced distress in EX vs. Control
  (p-value 0.03)

→ New: Achieved interventions effects seems to be sustainable

Conclusion

→ partly-supervised exercise intervention is beneficial
→ because of low personnel requirements it might be valuable to integrate
  such a program into standard medical care

PETRA-Study

Physical Exercise Therapy and Relaxation in Allogeneic stem cell transplantation

A Randomized, Controlled Intervention Study
Cooperation Partners: University Clinic Heidelberg, Department: Stem Cell Transplantation
Central Institute of Mental Health, Mannheim
Funding: German José Carreras Leukemia-Foundation e.V.

Clinical Trails.gov Identifier: NCT01374399
Aims PETRA-Study

- Feasibility of an one year exercise intervention in allo-HSCT
- 1-/2-years overall-survival
- Effects on clinical relevant symptoms (fatigue, QoL, GvHD incidence, infections, physical functioning)
- Hematological and immunological reconstruction

Design PETRA-Study

Inpatient setting
- Baseline diagnostic / admission
- Day 0
- Discharge
- Exercise (endurance and resistance training) 5x/week

Outpatient setting I
- Day 100
- Exercise (endurance and resistance training) 5x/week
- Day 180
- Relaxation (PM) 5x/week
- Day 270
- Exercise (endurance and resistance training) 5x/week
- Day 365
- Health care center / home-based

Outpatient setting II
- Day 0
- Exercise (endurance and resistance training) 5x/week
- T2
- Home-based
- T3
- Health care center / home-based
- T4
- T5
- T6
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Conclusion & Take Home Message

➢ Physical exercise is beneficial for patients undergoing HSCT
➢ PE has multidimensional effects
   (→ biopsychosocial perspective)
➢ Patients in „bad conditions“ benefits most

→ Larger RCTs with long-term interventions (to induce a stable physical active lifestyle) and follow-up periods are needed.
Thank you very much for your attention!

Acknowledgement

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