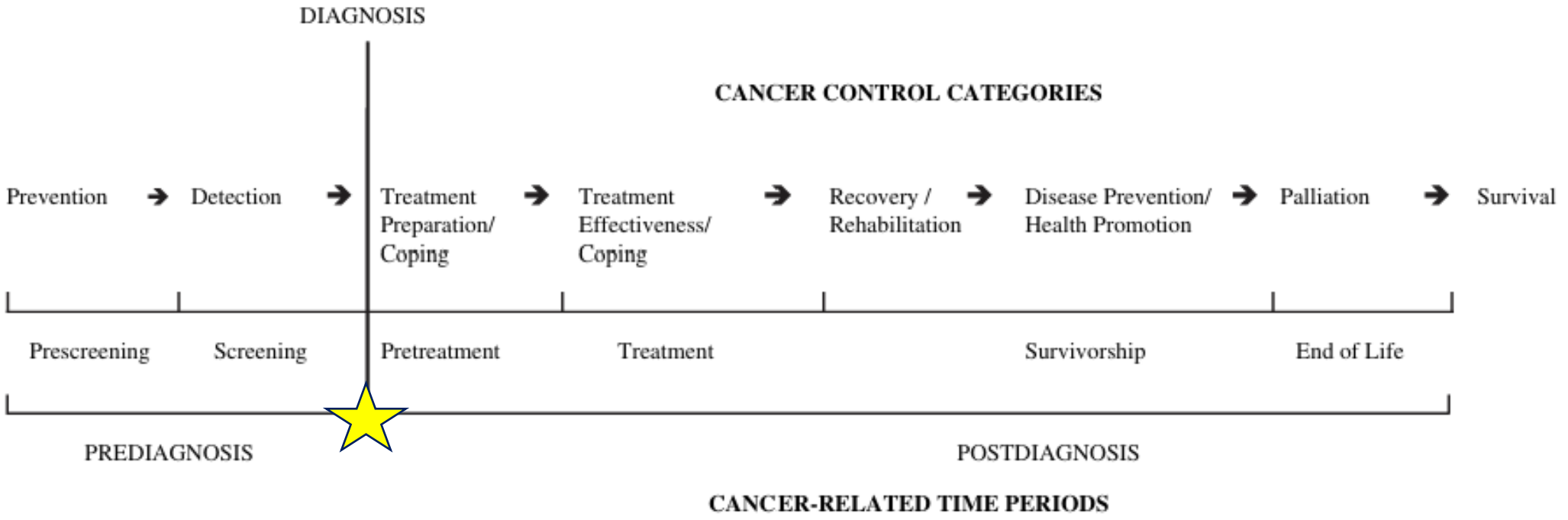

INTEGRATE
7.0
QUALI ‘REGOLE’ NELLA GESTIONE INTEGRATA
DELLA NEOPLASIA POLMONARE?
GAMES
VERONA
13-14 OTTOBRE
2025

Attività sportiva e riabilitazione nel paziente con neoplasia polmonare

Sara Pilotto
Section of Oncology,
Department of Engineering for Innovation Medicine
University of Verona

The Continuum of Care

Exercise and Nutrition Matter Before, During, and After Cancer



Exercise and nutrition are essential across the cancer continuum, from **prevention** to after diagnosis, as **prehabilitation**, **rehabilitation**, **survivorship,** and **palliation**

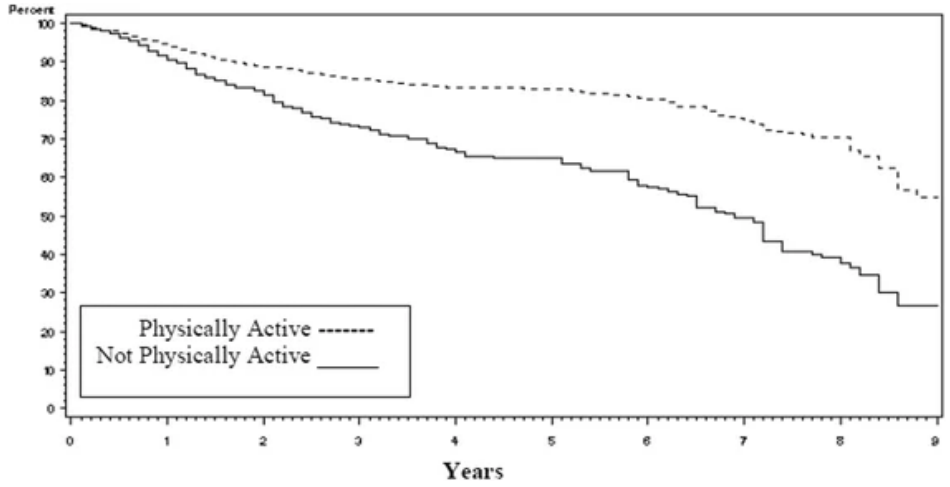
Cancer survivorship refers to the **phase of a person's life after a cancer diagnosis**, extending from the time of diagnosis throughout the remainder of their life. It includes anyone who has ever been diagnosed with cancer, **regardless of whether they are still undergoing treatment, in remission, or living with advanced disease**.

Courneya K. & Friedenreich C. Sem Oncol Nur 2007

Physical Activity & Cancer Outcomes

Epidemiological Evidence on Survival

Overall cohort

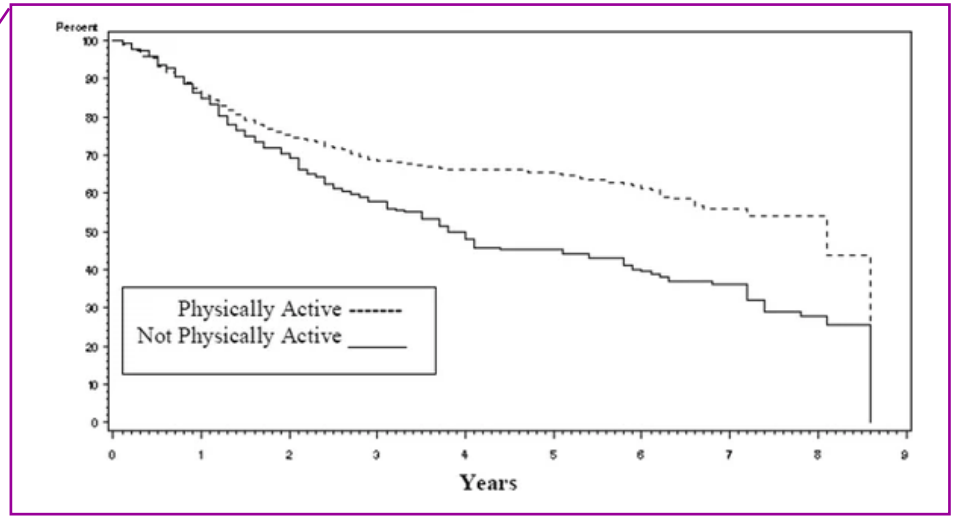


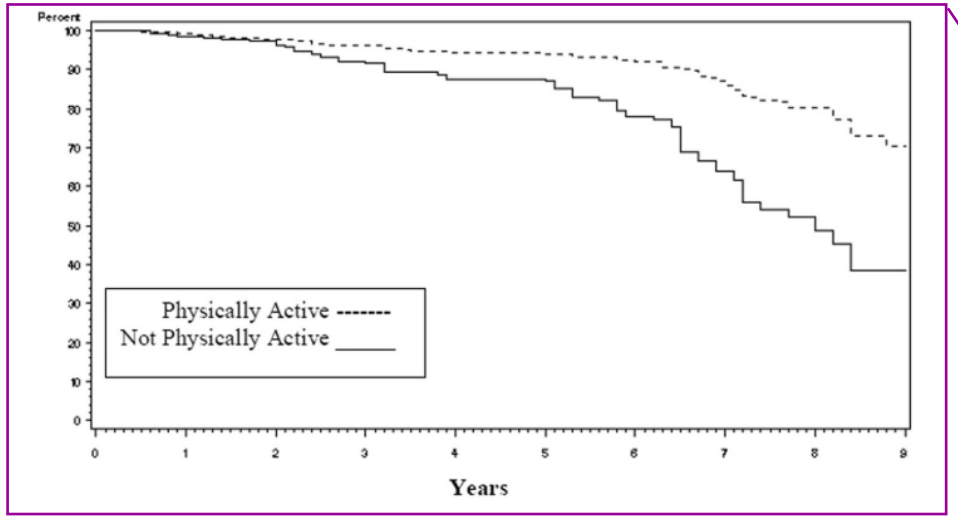
🧍♂️ Physically active patients → **+4 years survival** (8.4 vs 4.4 y, p < 0.0001)

📊 Effect consistent across:

- Disease stage: **early vs late**
- Cancer type: **NSCLC vs SCLC**

Advanced stage



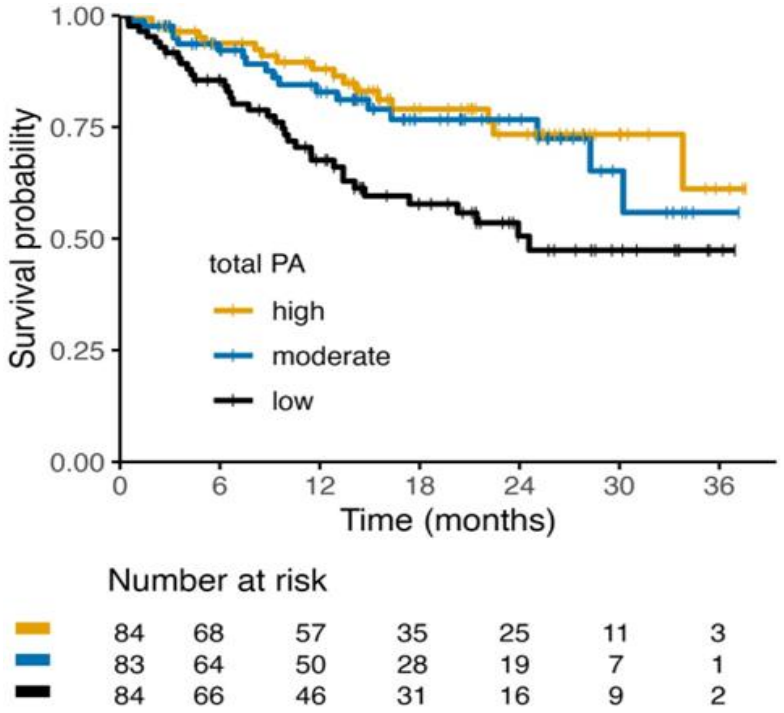


Early stage

Sloan J.A. et al. Health and Quality of Life Outcomes 2016

Physical Activity, Immunotherapy & Cancer Outcomes

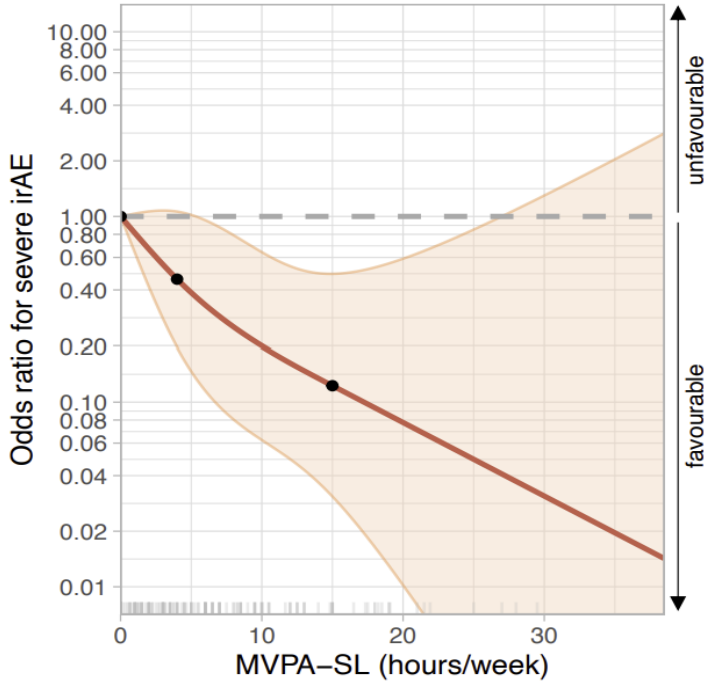
Epidemiological Evidence on Survival and Treatment-related Side Effects



Compared to patients with low levels of physical activity those reporting moderate or high levels

Have an improved OS

Have a lower risk of developing severe irAEs within 1y

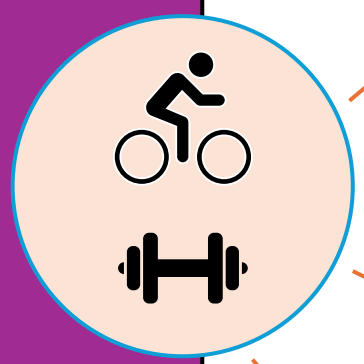


Verheijden R.J. et al. JNCI 2024

The Benefits of Physical Activity in Lung Cancer

Physical fitness, symptoms, and patient-reported outcomes

Physical Exercise
(planned, structured, and repetitive physical activity to maintain fitness and health)



- Cardiorespiratory fitness & pulmonary function
- Muscle mass and strength
- Symptoms & AEs (e.g., fatigue, dyspnea, pain, neuropathy)
- Mental health (e.g., anxiety depression)
- Quality of life

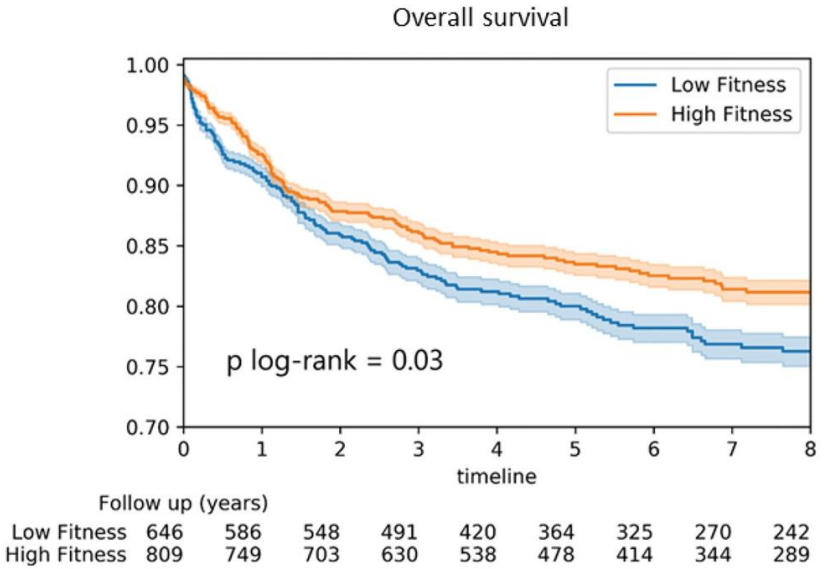
Avancini et al. Exp Rev Ant Ther 2021; Avancini A et al, The Oncologist 2020

Cardiorespiratory Fitness – More Than Just Training

A Key Prognostic Factor for Survival in Cancer Survivors

Cardiorespiratory fitness, i.e., the ability and efficiency of the body's circulatory and respiratory systems to supply oxygen to the muscles during sustained physical activity, is a ***strong prognostic factor***

	Total	Low CRF	Intermediate CRF	High CRF
All-cause mortality				
Number of events	229	143	58	28
Age-adjusted HR (95% CI)		Ref	0.44 (0.32–0.60)	0.26 (0.17–0.40)
Multivariable-adjusted HR (95% CI)		Ref	**0.38** (0.28–0.52)	**0.17** (0.11–0.27)
Cardiovascular mortality				
Number of events	50	32	10	8
Age-adjusted HR (95% CI)		Ref	0.39 (0.19–0.80)	0.45 (0.19–1.04)
Multivariable-adjusted HR (95% CI)		Ref	0.40 (0.19–0.86)	0.41 (0.16–1.05)
Cancer mortality				
Number of events	132	77	37	18
Age-adjusted HR (95% CI)		Ref	0.47 (0.32–0.71)	0.25 (0.14–0.43)
Multivariable-adjusted HR (95% CI)		Ref	0.38 (0.26–0.60)	0.16 (0.09–0.28)

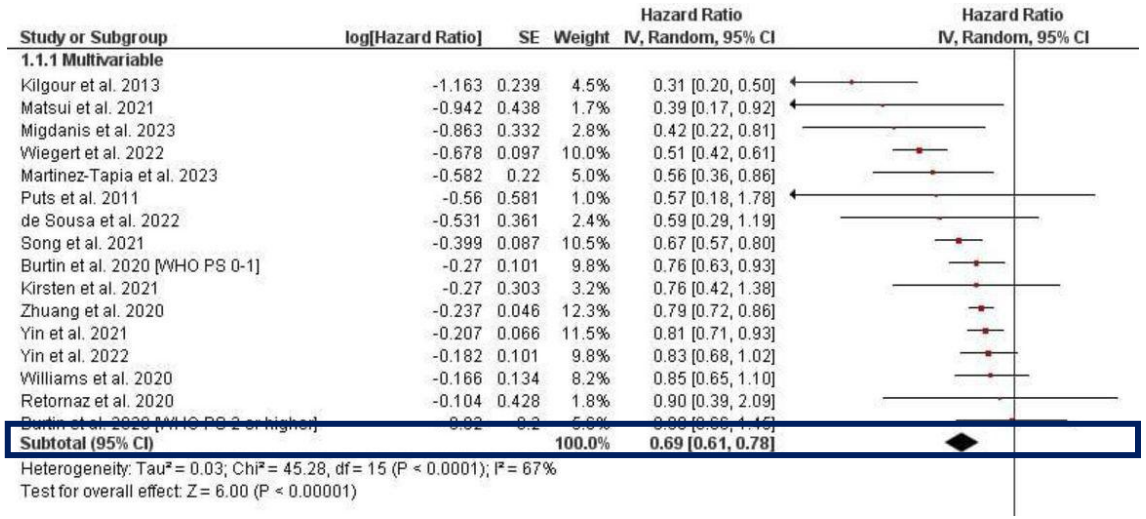


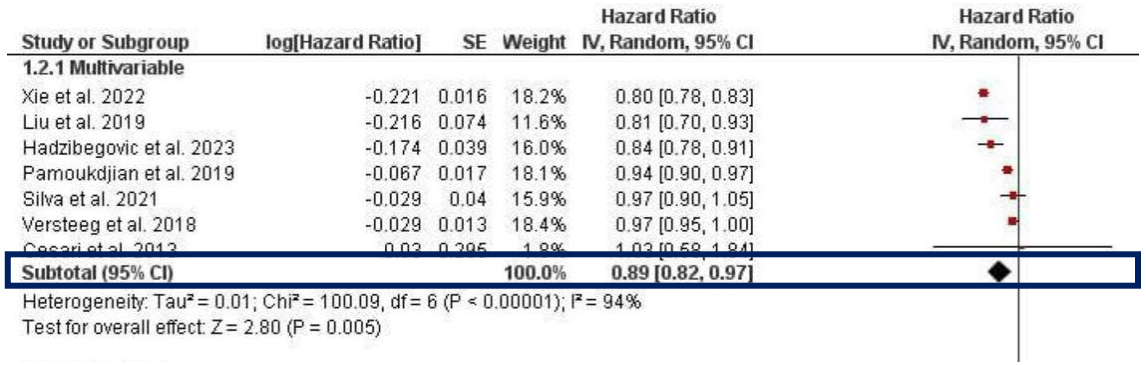
Each 1 MET gain:
↓ **26%** all-cause mortality
↓ **14%** CV mortality
↓ **25%** cancer mortality

Groarke et al. European Heart Journal 2020

Muscle Strength – Beyond Performance

A Key Prognostic Factor for Survival in Cancer Survivors





🏋️ High vs low muscle strength → ↓ **all-cause mortality 31–46%**

🔬 Benefits evident in advanced stages, lung & digestive cancers

❤️ Each ↑ in muscle strength → ↓ all-cause mortality 11%

🎯 Key message: **Tailored exercise to improve muscle strength may reduce cancer-related mortality**

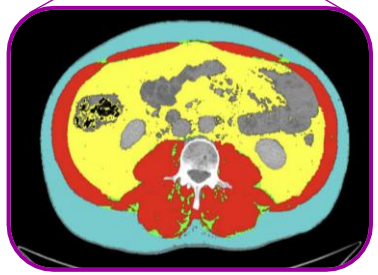
Bettariga et al. BJSM 2025

Sarcopenia – A Hidden Prognostic Marker

A Key Prognostic Factor for Survival in Cancer Survivors

134 patients with treatment-naïve NSCLC, median age 69y

Body composition assessment

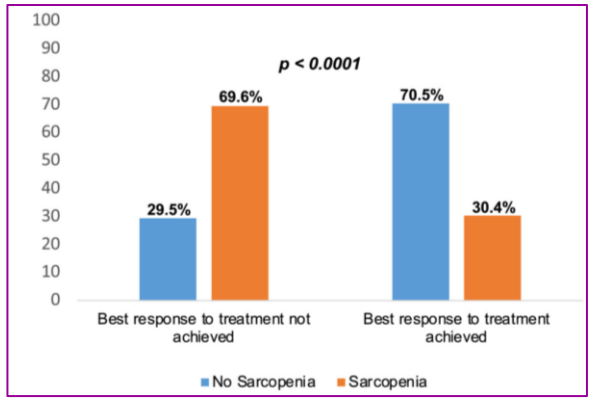


Median follow-up 12 months

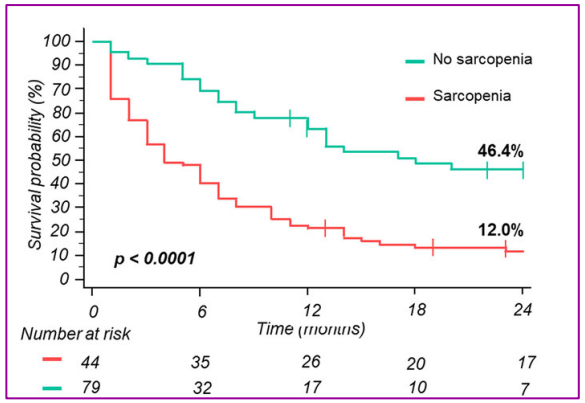
Pembrolizumab

- **Sarcopenia is a strong negative predictor of outcomes** across cancer types and stages (during and after treatment)

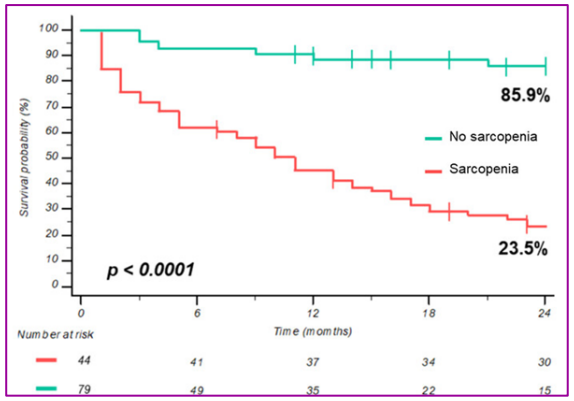
ORR



PFS



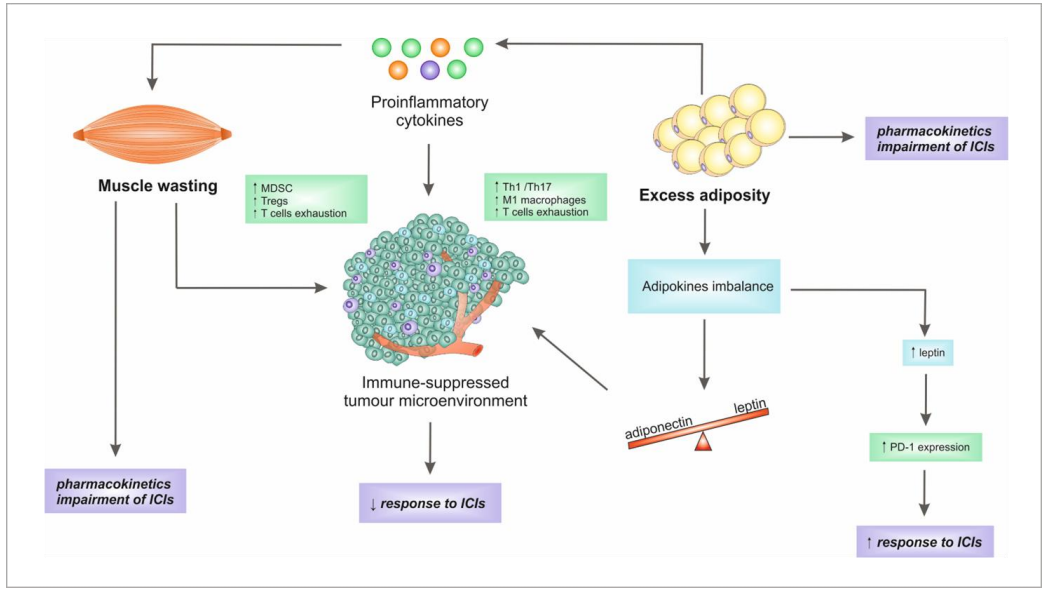
OS

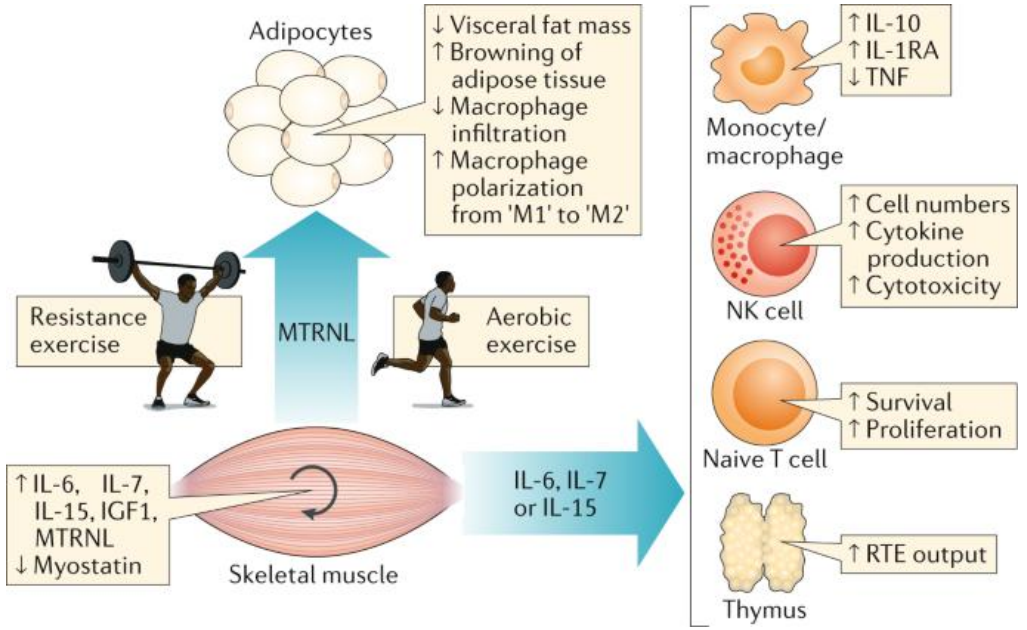


Trestini I. et al. Journal of Cachexia, Sarcopenia and Muscle 2024

Body Composition in Immuno-Oncology

Beyond BMI: impact of muscle and fat distribution





🧍♂️ Body composition matters → fat vs muscle differently impact IO efficacy

🧪 **Excess adiposity** → adipokine imbalance + chronic inflammation → ↓ ICI response

💪 **Muscle wasting** → impaired immune function & suppressed TME → ↓ ICI response

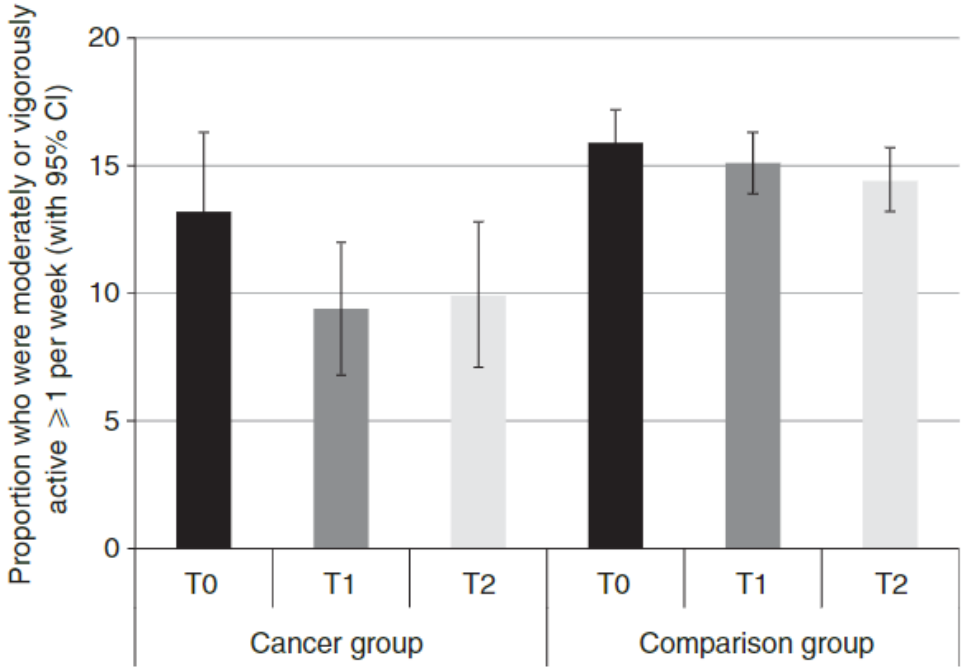
💪 **Muscle as an immune organ** → secretes myokines with autocrine, paracrine & endocrine effects

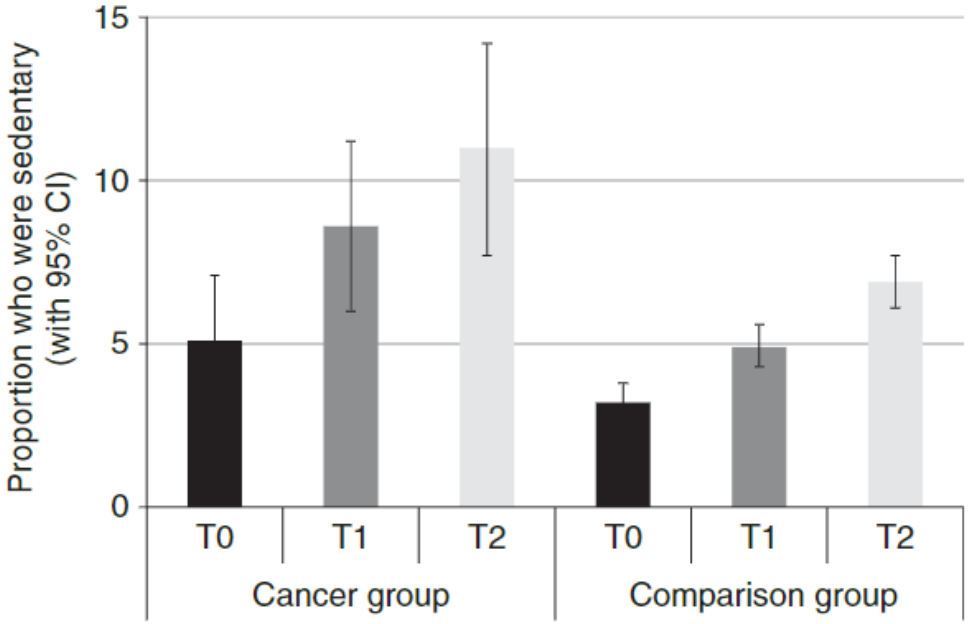
🧬 Key **myokines** (IL-6, IL-15, IL-7, IGF-1, MTRNL) → regulate inflammation, support T/NK cells, maintain thymic output, influence fat metabolism, and promote M2 macrophage polarization

Trestini I et al. ESMO Open 2021; Duggal NA, et al. Nat Rev Immunol 2019

Cancer Diagnosis – A Teachable Moment

Encouraging Positive Changes, Avoiding Harm





🏃 **Physical activity decreases** after cancer diagnosis compared to pre-diagnosis levels

🛋️ **Sedentary behaviour increases** after cancer diagnosis compared to pre-diagnosis levels

Williams K et al. British Journal of Cancer 2013

What Should Healthcare Providers Do?

An Approach for Everyday Clinical Practice

1st step
ASSESS

Identify **insufficiently active** patients

2nd step
ADVISE

Introduce the **importance** of exercise

Give suggestions according to the **guidelines**

3rd step
REFER

Refer inactive patients to an **exercise service**

Aims:
Promote the correct information

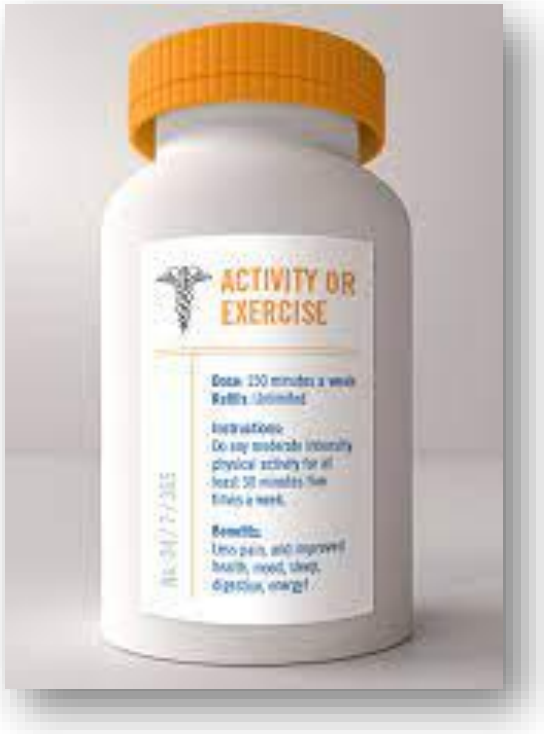
Decrease the rate of patients who are insufficiently active

Assess – Physical Activity

Recommended for All Cancer Patients at Diagnosis to Identify Physical Inactivity Early

Objective is to identify patients who are **insufficiently active**

How many days during the past week have you performed physical activity where your heart beats faster and your breathing is harder than normal for 30 minutes or more?							
0	1	2	3	4	5	6	7
How many days during the past week have you performed physical activity to increase muscle strength, such as lifting weights?							
0	1	2	3	4	5	6	7

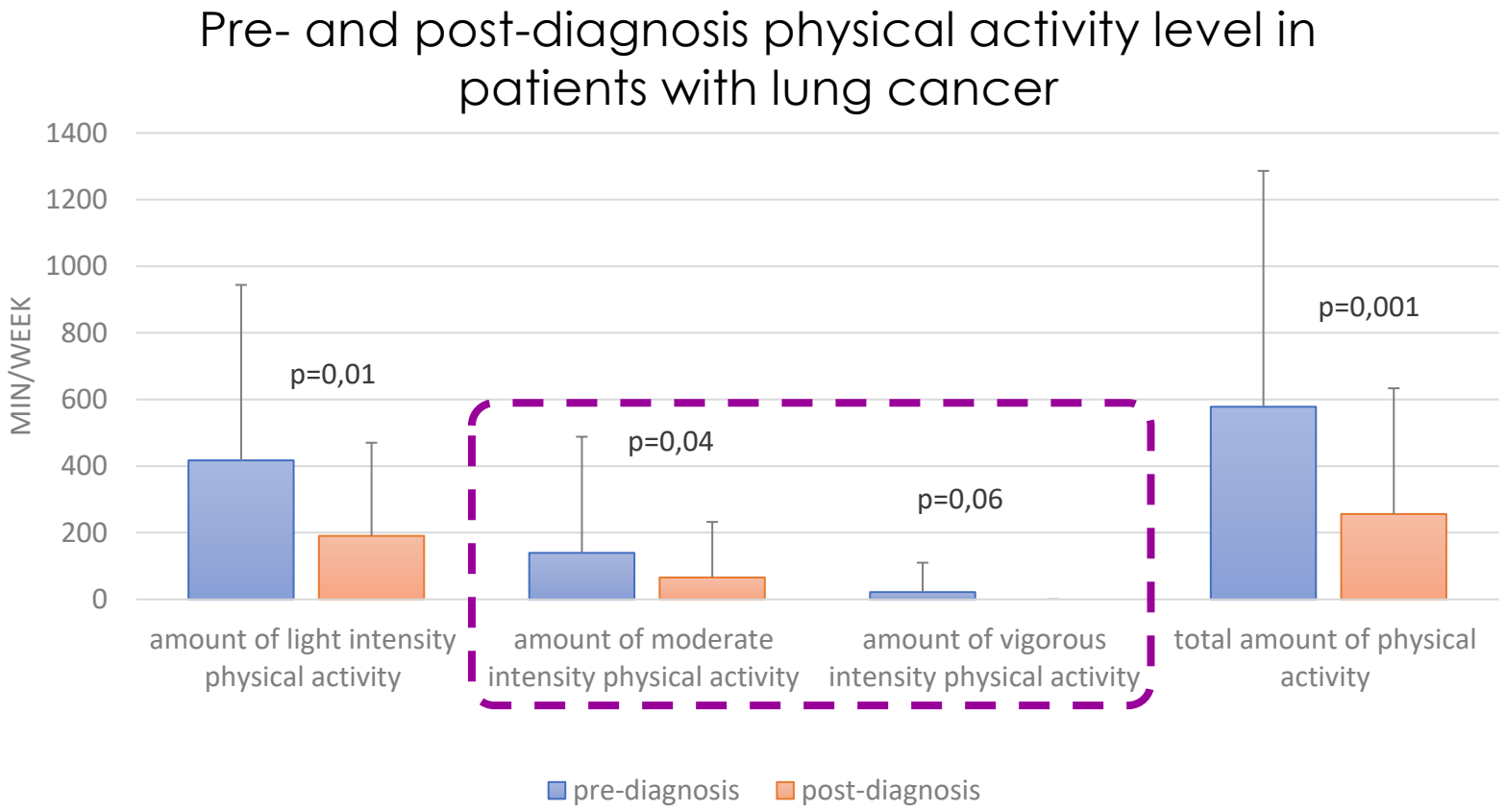


Physical Inactivity

Baseline Rates of Physical Inactivity in Patients with Lung Cancer

📊 Compared to pre-diagnosis:

- The proportion of patients who meet the exercise guidelines dropped from **14% to 3%**



Preliminary Data

How to Promote Physical Activity in Cancer?

Practical Advice for Patients and Survivorship Care

Aerobic activity

Types: cyclical activities such as walking, cycling, swimming
Frequency: 3 times/week
Duration: 30 minutes per session
Intensity: moderate/vigorous i.e., 60-80% HR max – 3-6 rate of perceived exertion CR10





Strength activity

Types: body weight exercise or using isotonic machines, involving the major muscle groups
Frequency: 2 times per week
Duration: 2 sets of 8-15 repetitions
Intensity: moderate/ vigorous i.e., 65-85% of the one maximum repetition



🔄 Exercise programs must be flexible and progressive, tailored to each patient's health status, side effects, and individual needs

Campbell et al. Med Sci Sports Exerc 2019

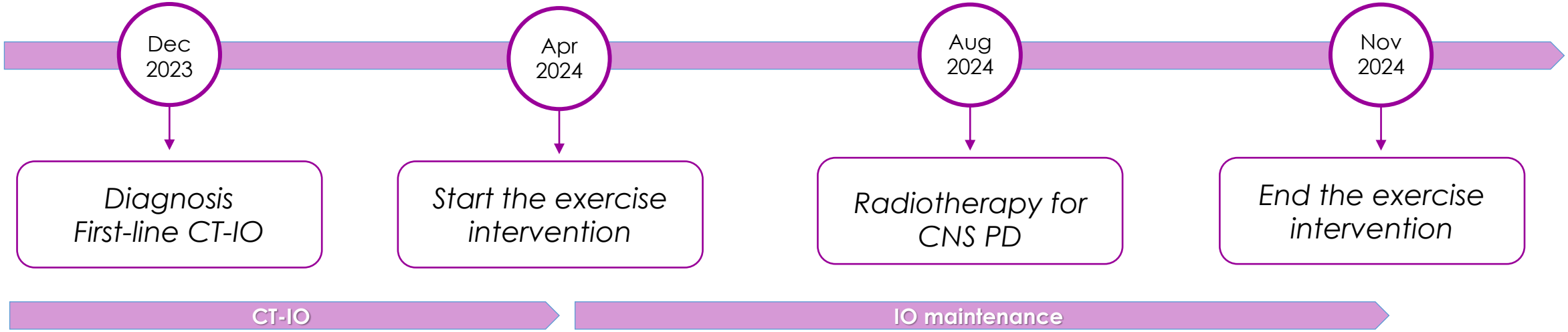
How to Manage Physical Inactivity in Cancer? – Refer

Early physical activity interventions to assess, prevent, and improve functional decline



Man, 66y old
Former smoker
169 cm, 75 kg → BMI 26.3

ED-SCLC (liver)

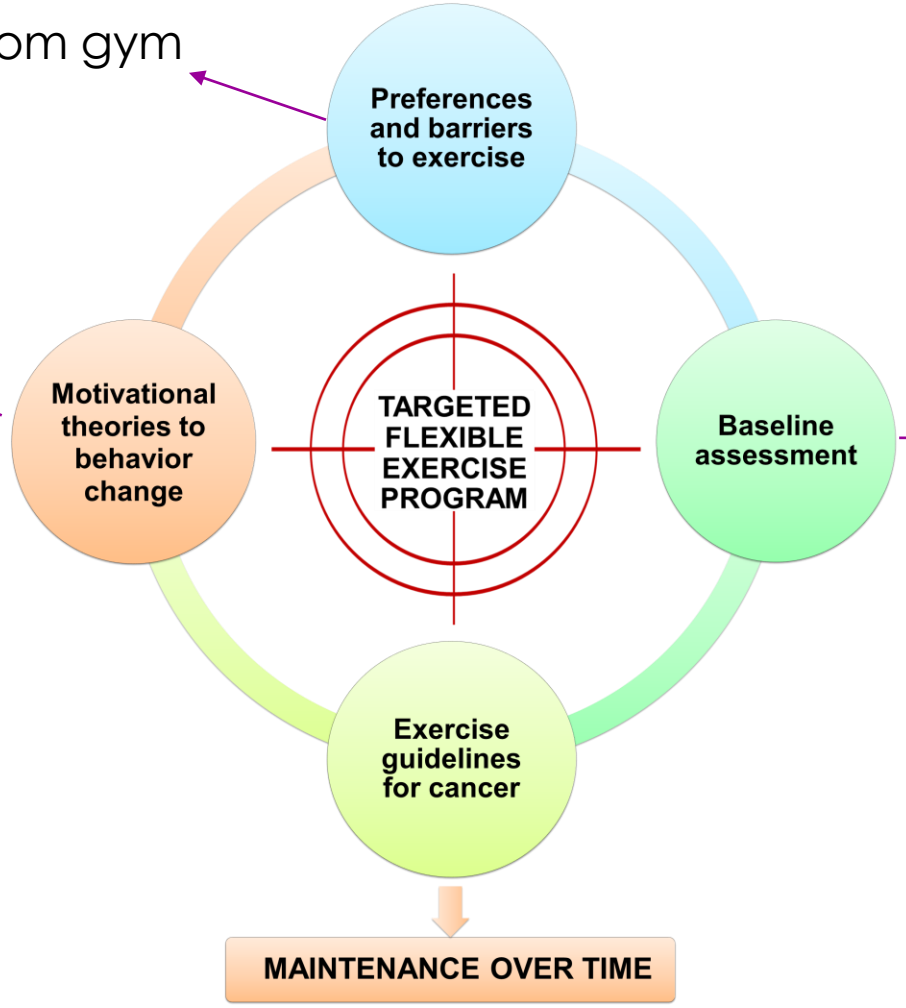


How to Manage Physical Inactivity in Cancer? – Refer

The baseline physical activity assessment

Distance from gym facility

e.g., goal setting (return to normal walk)



Health & Medical History + QoL + Fitness evaluation:

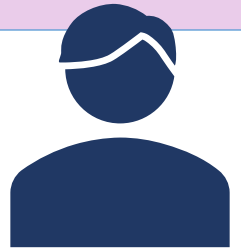
- Cardiorespiratory fitness (6MW)
- Flexibility (back scratch & chair sit and reach)
- Anthropometry + BIA analysis
- Upper limb strength (handgrip test)
- Lower limb strength (adapted!)

How to Manage Physical Inactivity in Cancer? – Refer

The baseline physical activity assessment

<u>Functional measures</u>:

- **Cardiorespiratory fitness** (6MWT, meters): ▼ 460 [normality range 570/695]
- **Handgrip strength test** (kg): ▼ 60 [normality range 102/109]
- **Isometric leg press strength test** (kg): ▼ 68.7 [normality range 156/178]
- **Upper limbs flexibility** (cm): ▼ -10.0 dx; ▼ -13.5 sx [normality range -10/ +2]
- **Lower limbs flexibility** (cm): ▼ -13.5 [normality range -10/ 0]
- **Waist/hip ratio** (cm): 0.93



How to Manage Physical Inactivity in Cancer? – Refer

The Program – 1-3 months



The exercise program

A program to perform twice a week under supervision of a specialized kinesiologist

Exercise session:

Warm-up at light intensity

10’ of dynamic stretching to improve joints range of motion

Cardiovascular activity at moderate intensity

10-25’ of aerobic exercise, duration progressively increased over the week

Strength exercise at moderate intensity

2-3 sets, 8-12 repetitions of six strength exercises

Cool-down at light intensity

Balance and static stretching



How to Manage Physical Inactivity in Cancer? – Refer

The Program – 1-3 months



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2-3 sets, 8-12 repetitions of six strength exercises

Cool-down at light intensity

Balance and static stretching



How to Manage Physical Inactivity in Cancer? – Refer

Assessments after 3 months

Measure	At baseline	3 months
Cardiorespiratory fitness	460	442
Upper strength	60	58
Lower strength	68.8	72
Upper flexibility	-28	-19
Lower flexibility	-14	-22
Waist/hip ratio	0.93	0.92

Measure	At baseline	3 months
Physical functioning	86.7	93.3
Role functioning	83.3	100.0
Emotional functioning	91.7	100.0
Cognitive functioning	100.0	100.0
Social functioning	100.0	100.0
Global health status	83.3	50.0
Fatigue	22.2	33.3
Nausea/vomiting	0.0	16.7
Pain	16.7	33.3
Dyspnea	33.3	66.7
Insomnia	33.3	66.7
Appetite loss	0.0	33.3
Constipation	33.3	0.0
Diarrhea	0.0	0.0
Financial problems	0.0	0.0

💪 Physical condition and symptoms slightly deteriorated

📈 Functional domains of QoL improved

How to Manage Physical Inactivity in Cancer? – Refer

The Program – 4-6 months

Isotonic machines











The exercise program

A program to perform twice a week under supervision of a specialized kinesiologist

Exercise session:

Warm-up at light intensity

10' of dynamic stretching to improve joints range of motion

Cardiovascular activity at moderate intensity

25-35' of aerobic exercise, duration progressively increased over the week

5 strength exercise at moderate intensity

2-3 sets, 8-12 repetitions of six strength exercises (months 6-9);

Cool-down at light intensity

Balance and static stretching



How to Manage Physical Inactivity in Cancer? – Refer

Final assessment

Measure	At baseline	3 months	6 months
Cardiorespiratory fitness	460	442	480
Upper strength	60	58	65
Lower strength	68.8	72	85
Upper flexibility	-28	-19	-18
Lower flexibility	-14	-22	-11
Waist/hip ratio	0.93	0.92	0.92

All physical parameters improved, above the baseline assessments

How to Manage Physical Inactivity in Cancer? – Refer

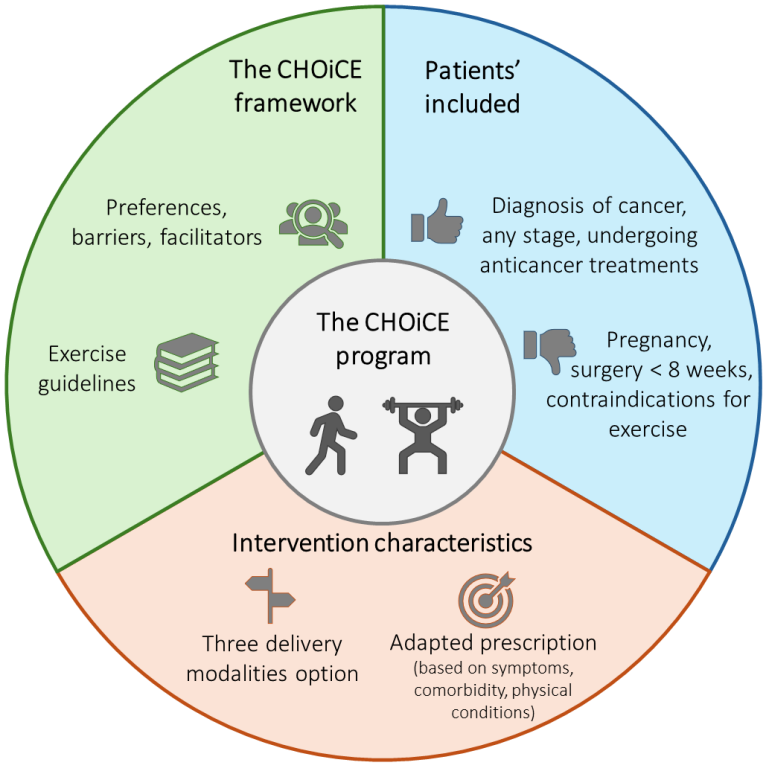
Final assessment

Measure	At baseline	3 months	6 months
Physical functioning	86.7	93.3	93.3
Role functioning	83.3	100.0	100.0
Emotional functioning	91.7	100.0	100.0
Cognitive functioning	100.0	100.0	100.0
Social functioning	100.0	100.0	100.0
Global health status	83.3	50.0	86.7
Fatigue	22.2	33.3	11.1
Nausea/vomiting	0.0	16.7	0.0
Pain	16.7	33.3	16.7
Dyspnea	33.3	66.7	16.7
Insomnia	33.3	66.7	33.3
Appetite loss	0.0	33.3	0.0
Constipation	33.3	0.0	0.0
Diarrhea	0.0	0.0	0.0
Financial problems	0.0	0.0	0.0

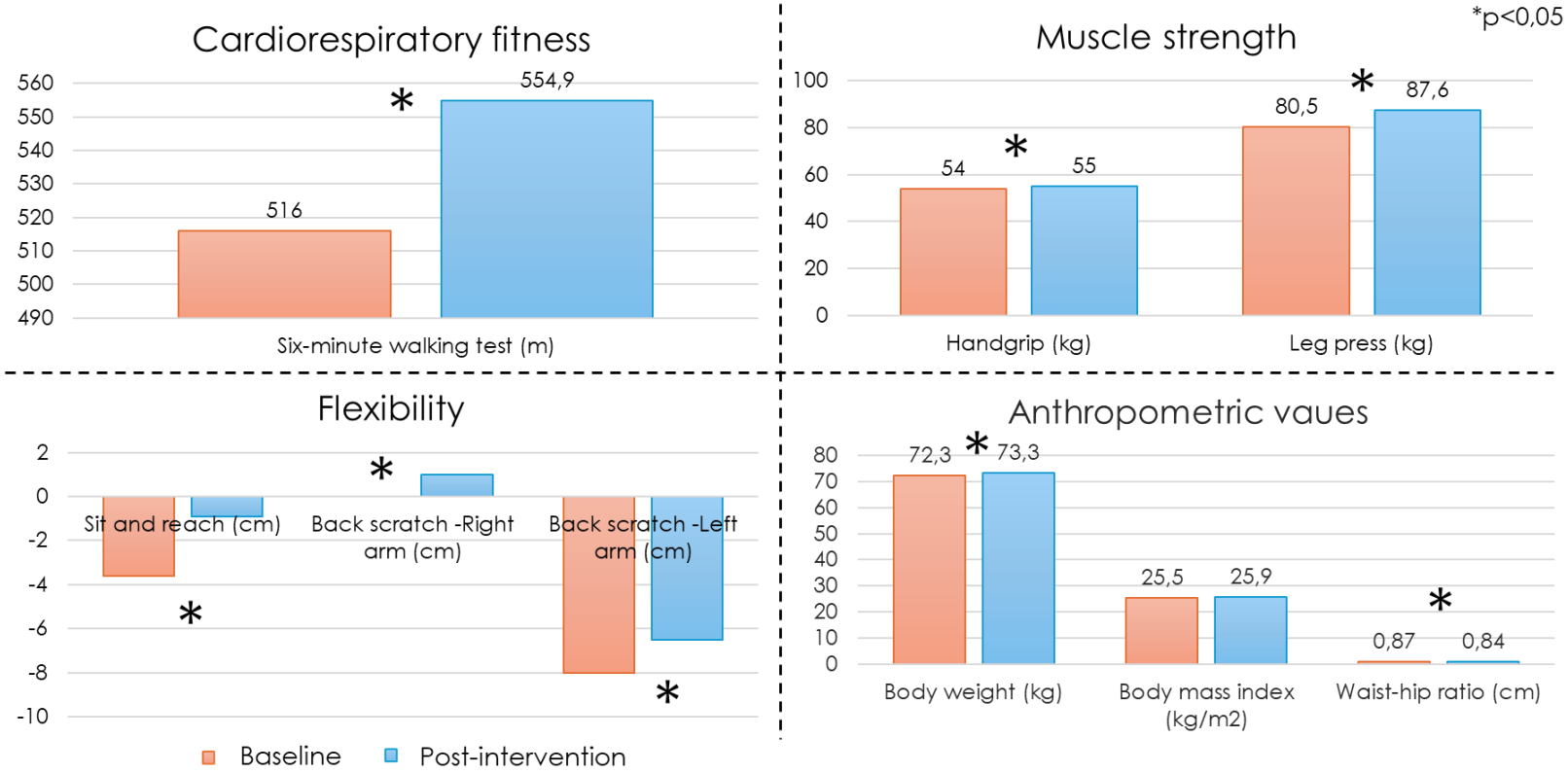
Personalized Exercise During Treatment: Feasibility & Effectiveness

CHOiCE Prospective Study Results

214 patients were referred, 34 were excluded mainly because they did not meet the eligibility criteria.
180 patients (gastrointestinal 38%, breast cancer 34% - advanced 49%)



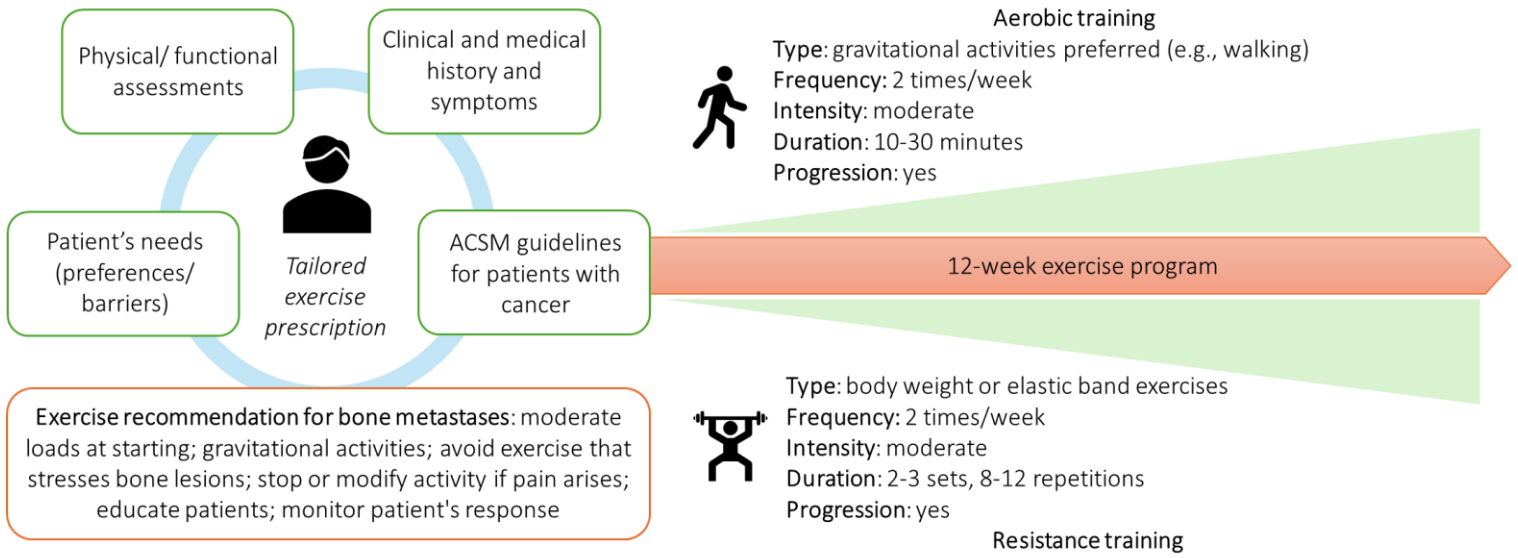
After 3 months



Avancini A et al, under review

Personalized Exercise During Treatment: Feasibility & Effectiveness

The case of bone metastases



21 patients, 58.7y mean age, 68% female, 29% lung cancer, 90% multiple bone metastases, 52% osteolytic lesions

Adherence

🏠 Home-based program: 90%

🏢 In-person program: 89%

📊 **Overall: 85%**

Safety

✅ No G ≥3 AEs related to exercise

✅ ↑ functional capacity

❌ ↔ muscle strength

✅ ↑ QoL physical, role, emotional functioning

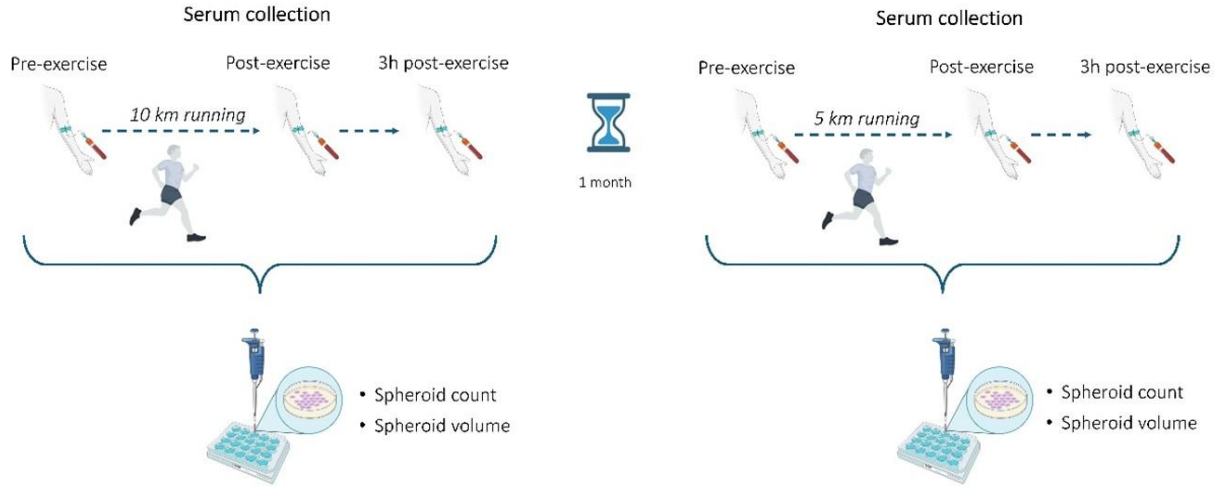
✅ ↓ QoL fatigue, appetite loss

Borsati A et al, EJCC 2025

Even a Single Exercise Session Matters

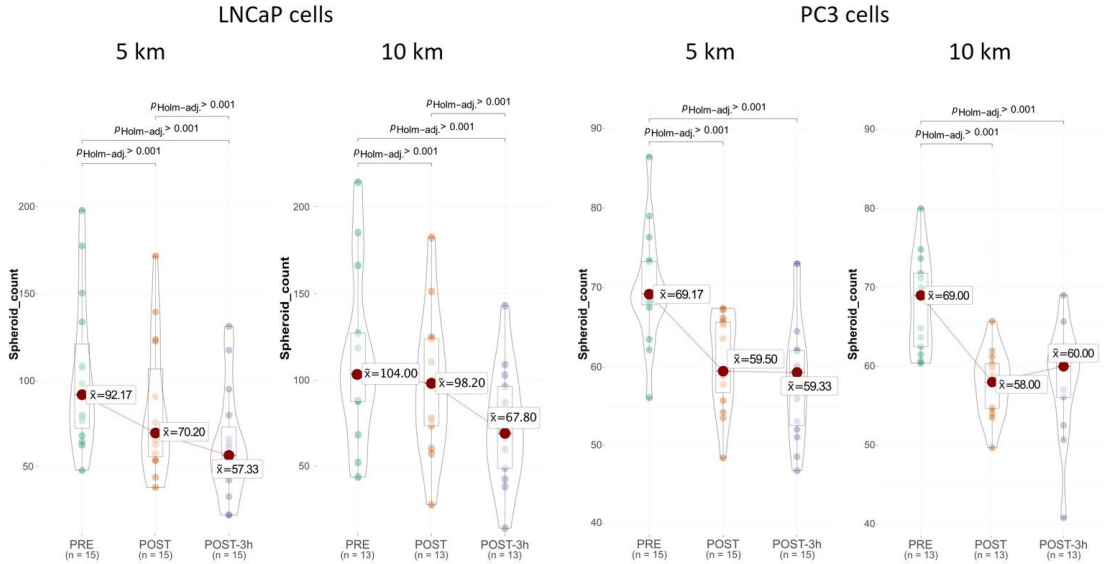
Preclinical Implications

- 🧍♂ 13 healthy donors (47.7 ± 16.1 yrs)
- 🏃 Two running sessions: 5 km & 10 km
- 💉 Blood collection: PRE, POST, POST 3h
- 🧫 Serum tested on LNCaP & PC3 PC cells
- 🔬 Outcome: spheroid number & volume



Spheroid number in LNCaP:

- After exercise 5km **-23.8%;** 10km: **-5.6%;**
- 3 hours post-exercise: 5km: **-37.8%**; 10km: **-34.8%**



Spheroid number in PC3:

- After exercise 5km **-14%;** 10km: **-15.9% ;**
- 3 hours post-exercise: 5km: **-14.2%;** 10km: **-13%**

Baldelli G et al, J. Can Res Clin Onc. 2025

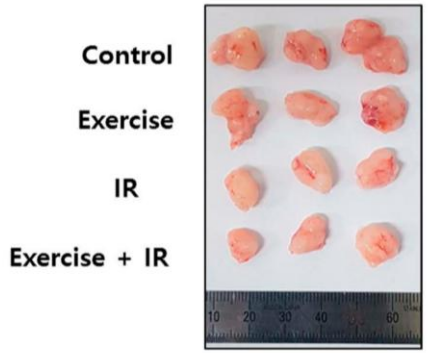
Exercise and radiotherapy: a synergist effect?

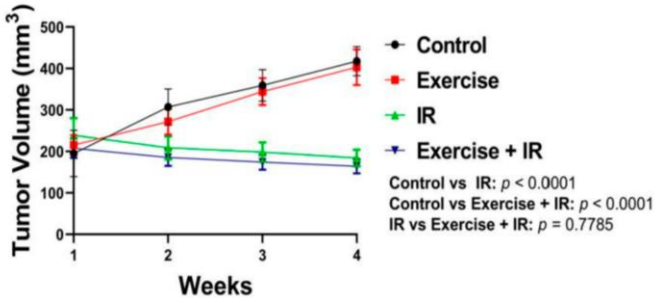
Evidence from preclinical NSCLC models

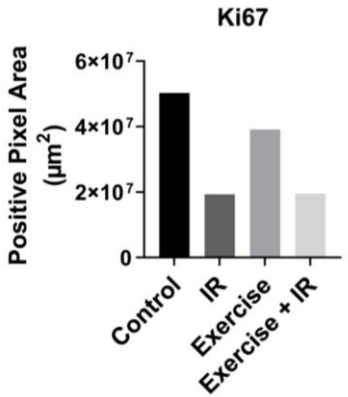
⚗️ **2. Experimental Groups** (n = 5 mice each): **Control** – no EX, no RT; **EX** – 30 min/session, 3 t/w, for 2 weeks; **RT** – 2 Gy/fr, 6 fr; **EX + RT**

🫧 **Tumor Growth - EX + RT**

- ↓ tumor growth ➡️ enhanced antitumor efficacy when EX + RT
- ↑ **necrotic areas** and **disorganized tumor structure** in EX + RT







🔬 **IHC – EX + RT**

- ↓ **Ki-67** → reduced cellular proliferation after combined treatment
- ↑ **HIF-1a & ↑ CA IX** → adaptive response to fluctuating O_2 dynamic modulation of tumor oxygenation rather than persistent hypoxia
- ↑ **DHE staining** ➔ enhanced oxidative stress

🧬 **Gene Expression- EX +RT:** 179 genes up-regulated and 156 down-regulated; ➡️ activation of antioxidant and redox-detoxification pathways and increased mitochondrial stress and a higher tendency toward apoptosis

🧠 **Interpretation:**
EX acts as a physiological radiosensitizer, promoting tumor cell apoptosis and enhancing RT efficacy

Jo et al., Int. J. Mol. Sci. 2024

A New Era for Lifestyle Interventions?

The CHALLENGE study

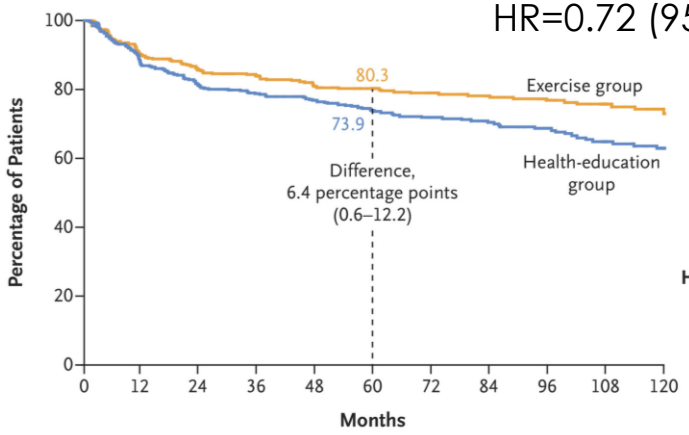
889 patients with resected stage III after adj chemo → R 1:1

INTERVENTION: 3-year of aerobic exercise at moderate to vigorous intensity – 150 min week

CONTROL: educational materials

Primary endpoint: DFS
Secondary endpoints: OS, safety, cardiorespiratory fitness, QoL

80.3 % IC vs 73.9 % CG;
HR=0.72 (95 % CI 0.55–0.94)

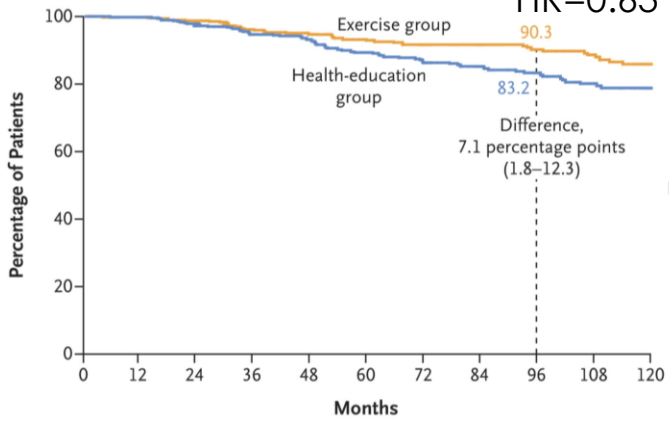


	Total Patients	Patients with Disease Recurrence, New Primary Cancer, or Death
		no.
Exercise Group	445	93
Health-Education Group	444	131

Hazard ratio, 0.72 (95% CI, 0.55–0.94)
2-sided P=0.02

No. of Patients											
Exercise group	445	378	336	301	278	254	229	190	159	119	58
Health-education group	444	374	326	295	272	239	213	178	142	107	53

90.3 % IC vs 83.2 % CG;
HR=0.63 (95 % CI 0.43–0.94)



	Total Patients	Patients Who Died
		no.
Exercise Group	445	41
Health-Education Group	444	66

Hazard ratio, 0.63 (95% CI, 0.43–0.94)

No. of Patients											
Exercise group	445	428	397	349	331	298	267	225	188	141	71
Health-education group	444	431	394	359	335	294	260	218	176	134	59

💪 **Exercise as a true adjuvant strategy in colorectal cancer care -** enhances treatment efficacy, improves functional capacity and quality of life, and can be safely integrated into standard care

Courneya et al, NEJM 2025

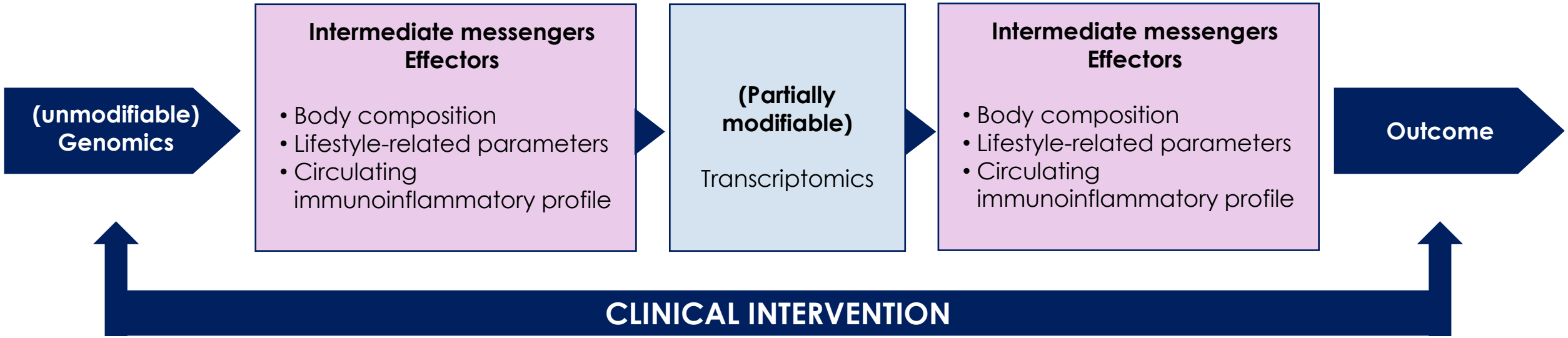
The STARLighT study

A perSonalized nuTrition and physicAl exeRcise intervention to enhance early-stage NSCLC ouTcomes

Thanks to **AIRC *NEXT GEN CLINICIAN SCIENTIST [from July 2024]***

The STARLighT Project

Hypotheses & Aims

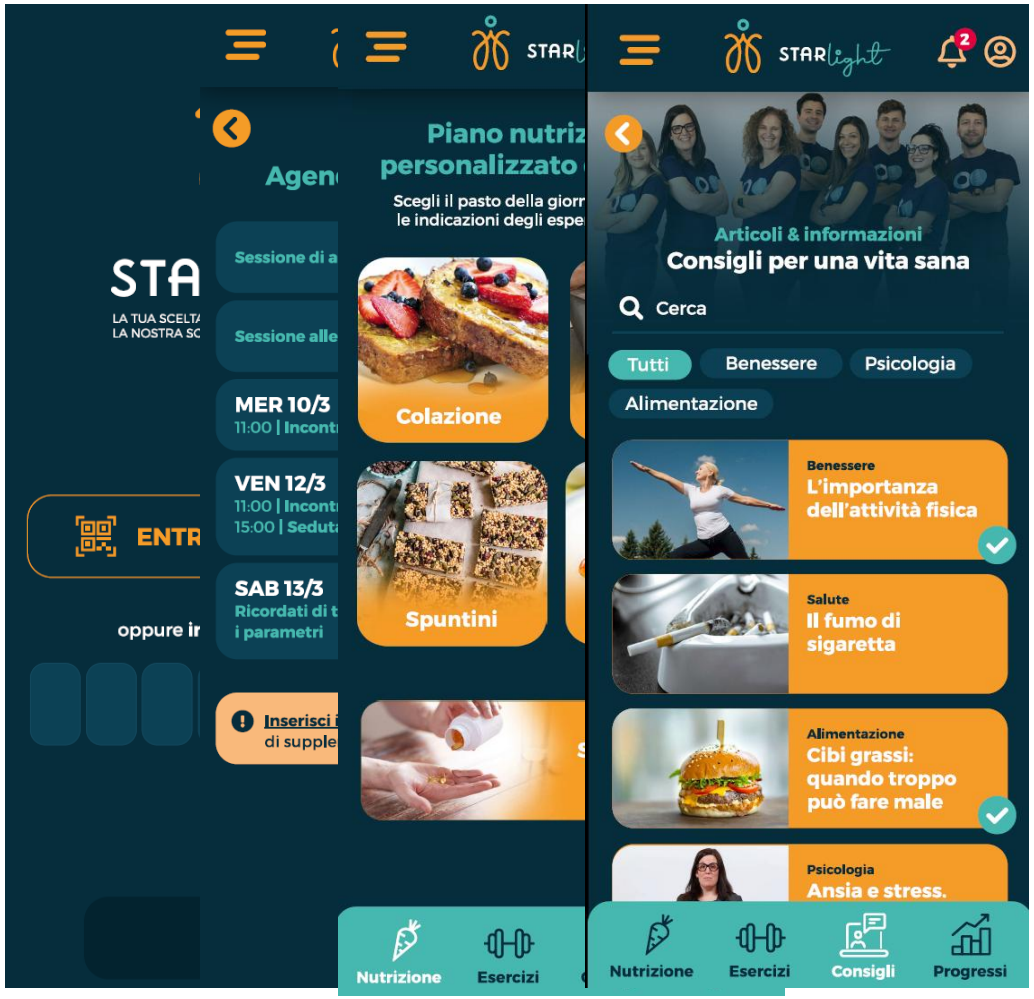


Testing the impact of a ***structured, evidence-based lifestyle intervention*** in early-stage lung cancer

Understanding the ***biological*** and ***molecular mechanisms*** of action of lifestyle interventions

The STARLighT Project

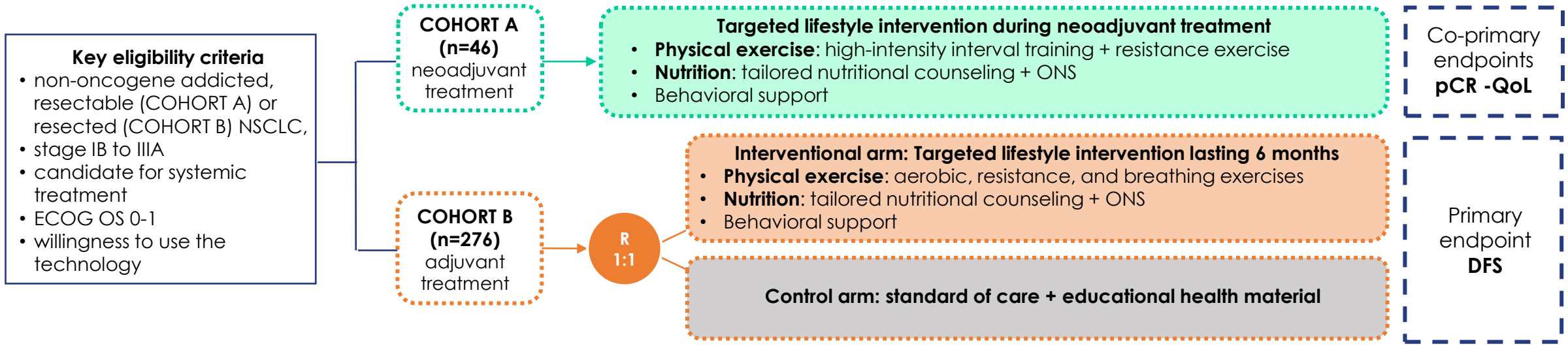
WP1 - Telehealth clinical intervention interface





The STARLighT Project

WP2 – Clinical trial



Secondary endpoints: treatment toxicities, feasibility of the intervention, OS, ORR, DCR, TTD, quality of life, immune-inflammatory status, fecal microbiota, functional capacity, muscle strength, body composition, physical activity, cardiorespiratory fitness, sarcopenia risk, malnutrition risk, psychological distress, anxiety and depression levels, sleep habits, cost-utility, and cost-effectiveness.

The STARLighT Project

WP3 - Investigating the link between Omics

Genomic Transcriptomics

Cohort A

Baseline sample (biopsy)

Neoadj + surgery

Surgical specimen

Cohort B

Baseline (surgical specimen)

Comprehensive genomic sequencing

Whole transcriptome analysis

Baseline & post-intervention

Immuno Inflammation

Immunophenotyping
Multiparametric FACS analysis:
- T lymphocyte subsets:
- B lymphocytes subsets
- NK lymphocytes
- Monocyte subsets
- IDO1, ARG1, c-FLIP, and VISTA ex in M-MDSCs

T cell repertoire
Adaptive Biotechnologies
immunoSEQ assay

Monocyte gene signature
RNA-seq on $CD14^+$ cells

Soluble factors
Multiplex ELISA on plasma samples
Evaluation of CRP, LDH and others clinical parameter

Gut Microbiota

Who: Cohort A + patients undergoing ICIs in cohort B
When: Before and after the lifestyle intervention



After 6 months of tailored lifestyle intervention:

"At the beginning of my disease journey, I was going to the hospital in wheelchairs, I couldn't walk without experiencing terrible pain, I was losing weight day after day…then, together with the oncological treatment, I started physical exercise and an adequate diet delivered by dedicated experts ***and progressively I returned to walk again, I gained weight, strength, but, above all, again will to live and trust to the future."***



Marilena (56 yo), affected by metastatic NSCLC treated with IO
(during a focus group dedicated to patients with bone mets)

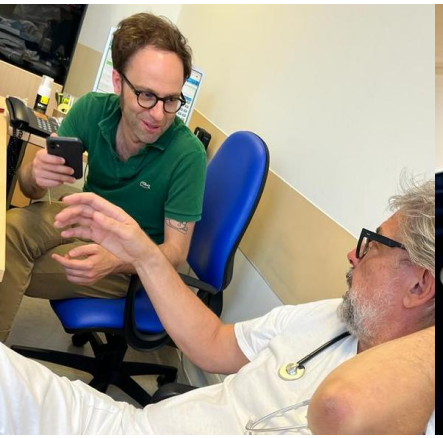
Team dedicated to thoracic malignancies:

- Sara Pilotto
- Lorenzo Belluomini
- Marco Sposito
- Jessica Insolda
- Jessica Menis
- Ilaria Scaglione
- Michele Rota
- Serena Eccher
- Luca Pasqualin
- Federico Sganzerla

FORCE Team:

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- Ilaria Trestini
- Daniela Tregnago
- Federico Schena
- Anita Borsati
- Christian Ciurnelli
- Linda Toniolo
- Matteo Ferri
- Matteo Lovo

& a visionary Mentor Prof. Milella










Thank you for your Attention!

Follow the STARLighT on LinkedIn!!!!