PHYSICAL ACTIVITY, EXERCISE AND CANCER

REVIEW ARTICLE

From muscle contraction to tumour control: Exercise as an immunometabolic and supportive therapy in oncology

Ivana Grle. *Department of Physical Medicine and Rehabilitation. University Clinical Hospital Mostar. Mostar, Bosnia and Herzegovina.*
Maki Grle. *Department of Orthopaedics. University Clinical Hospital Mostar. Bosnia and Herzegovina.*
Jerko Prlić. *Department of Orthopaedics. University Clinical Hospital Mostar. Bosnia and Herzegovina.*
Dejan Tiric. *Department of Obstetrics and Gynecology. University Clinical Hospital Mostar. Bosnia and Herzegovina.*
Bozenka Galic Tiric. *Chair of Occupational Medicine. Faculty of Medicine. University of Mostar. Bosnia and Herzegovina.*
Jasmin Budimlić. *Deparment of Physical Education and Sport. Faculty of Pedagogy. University of Bihać. Bosnia and Herzegovina.*
Nijaz Skender. *Deparment of Physical Education and Sport. Faculty of Pedagogy. University of Bihać. Bosnia and Herzegovina.*
Mate Vukoja. *Golden Darts d.o.o. Croatia.*
Boriss Bazanov. *Tallin University. Estonia.*
Ivica Franjko. *Faculty of Kinesiology Osijek. Josip Juraj Strossmayer University of Osijek. Croatia.*
Ahmet Naci Dilek. *Faculty of Sport Science. Bartın University. Türkiye.*
Ivan Đuroci. *Faculty of Kinesiology. University of Zagreb. Croatia.*
Besnik Morina. *Faculty of Physical Education and Sport. University of Pristina "Hasan Pristina". Kosovo.*
Davor Ljesević. *Faculty of Kinesiology. University of Zagreb. Croatia.*
Goran Sporiš ✉ **.** *Faculty of Kinesiology. University of Zagreb. Croatia.*
Patricia Zupanc. *Faculty of Kinesiology. University of Zagreb. Croatia.*
Adem Preljević. *State University of Novi Pazar, Sport and Physical Education. Serbia.*
Goran Špaleta. *Gym4you d.o.o. Croatia.*
Ernest Šabić. *Faculty of Pedagogy. University of Bihać. Bosnia and Herzegovina.*

ABSTRACT

Exercise is increasingly positioned as an adjunct to oncology care, yet its clinical benefits and proposed antitumour mechanisms are often discussed in parallel rather than as a unified biological model. This focused mini review integrates 20 unique full-text sources spanning meta-analyses, systematic and narrative reviews, consensus guidance, and translational studies. The evidence supports a multiscale framework in which muscle contraction generates acute neuroendocrine and myokine signals, improves tumour perfusion and oxygenation, alters metabolite competition within the tumour microenvironment, mobilises cytotoxic immune cells, and preserves host muscle and functional reserve. Clinical evidence is strongest for improvements in cardiorespiratory fitness, strength, fatigue, physical function, and quality of life, whereas direct tumour control and enhancement of immunotherapy remain supported mainly by preclinical and early human mechanistic data. Important tensions include the context-dependent biology of interleukin-6, the distinction between vascular normalisation and tumour-promoting angiogenesis, the uncertain optimal exercise dose, and the risk that excessive energy expenditure may be inappropriate in severe cachexia. We propose a precision exercise oncology model that matches modality and dose to tumour phenotype, treatment phase, symptoms, physiological reserve, and dynamic monitoring. Exercise should be treated as evidence-based supportive care with plausible disease-modifying potential, not as a substitute for anticancer therapy.

Keywords: myokines; cancer cachexia; vascular normalisation; immune checkpoint inhibition; precision rehabilitation.

Cite this article as:
Grle, I., Grle, M., Prlić, J., Tiric, D., Tiric, B. G., Budimlić, J., … Šabić, E. (2026). From muscle contraction to tumour control: Exercise as an immunometabolic and supportive therapy in oncology. *Physical Activity, Exercise and Cancer*, 3(2), 115-128. https://doi.org/10.55860/MWXE3541

✉ **Corresponding author.** *Faculty of Kinesiology. University of Zagreb. Croatia*.
E-mail: goran.sporis@kif.unizg.hr
Submitted for publication June 18, 2026.
Accepted for publication July 28, 2026.
Published September 19, 2026.
Sustainability and Sports Science Journal. ISSN 2990-2975.

Identifier: https://doi.org/10.55860/MWXE3541

INTRODUCTION

Exercise oncology has moved beyond the question of whether patients with cancer can exercise safely. The more consequential question is how exercise should be deployed across the cancer continuum and which biological processes it can realistically modify. Consensus guidance supports avoiding inactivity and using aerobic, resistance, or combined exercise to improve fatigue, physical function, anxiety, depressive symptoms, and health-related quality of life (Campbell et al., 2019). More recent syntheses similarly position resistance and concurrent training as central components of supportive care, with clinically meaningful gains in strength and cardiorespiratory fitness (Castañeda-Babarro & Martinez Aguirre-Betolaza, 2026; Madeira et al., 2025).

At the same time, mechanistic exercise oncology has proposed that a contracting skeletal muscle is not merely a target of rehabilitation but an endocrine and metabolic organ capable of signalling to tumours and immune cells. Acute catecholamine release, contraction-induced myokines, altered substrate availability, vascular shear stress, improved oxygen delivery, and immune-cell redistribution provide plausible links between a bout of exercise and changes in tumour biology (Hojman et al., 2018; Li et al., 2026). Translational studies have reported exercise-conditioned serum suppressing breast cancer cell viability through beta-adrenergic and Hippo-YAP signalling, voluntary running mobilising natural killer cells through epinephrine and interleukin-6, and aerobic exercise improving tumour perfusion and chemotherapy response in murine models (Betof et al., 2015; Dethlefsen et al., 2017; Pedersen et al., 2016).

These findings are compelling but create a risk of overtranslation. The evidence that exercise improves patient-centred outcomes is substantially more mature than the evidence that it directly controls human tumours or sensitises them to systemic therapy. Moreover, tumour type, treatment phase, baseline fitness, cachexia, neuropathy, cardiovascular reserve, and the exercise dose can each alter the direction or magnitude of response. The purpose of this mini review is therefore to integrate the clinical and mechanistic literatures into one critical framework, distinguish established benefits from emerging hypotheses, and outline a precision model for exercise prescription in oncology.

Review approach

This focused evidence synthesis was based exclusively on the full-text articles supplied for the review. Twenty-one PDF files were received. File-level comparison identified one exact duplicate of the same 2025 Exercise Immunology Review article; the duplicate was removed, leaving 20 unique sources for synthesis.

The evidence set included consensus guidance, systematic reviews and meta-analyses, umbrella reviews, narrative and mechanistic reviews, an editorial synthesis, and translational cell, animal, and early human studies. Each source was mapped by population or model, exercise modality, biological or clinical outcome, principal contribution, and major limitation. Evidence was then organised into five convergent domains: acute endocrine and myokine signalling; tumour vascular and metabolic remodelling; immune mobilisation and immunotherapy; skeletal-muscle preservation and cachexia; and clinical implementation.

Because the supplied corpus was intentionally selected rather than generated through a reproducible database search, this article is a focused mini review and not a systematic review. No pooled re-analysis was performed. Quantitative findings are reported only when provided by the included sources. The maturity of evidence is described qualitatively as clinically established, clinically supportive, early translational, or predominantly preclinical; these labels are interpretive and do not constitute a formal GRADE assessment.

Table 1. Characteristics and critical contribution of the included evidence sources.

Source	Design / population or model	Exercise / focus	Principal contribution	Main caveat
Madeira et al., 2025	Systematic review/meta-analysis; 14 breast cancer survivor studies	Concurrent aerobic + resistance training	Improved body mass, strength and VO_2; fat-mass effect not significant	Protocol reporting and disease-stage heterogeneity
Herranz-Gómez et al., 2022	Umbrella review/meta-meta-analysis; 7 systematic reviews	HIIT across cancer populations	Small CRF benefit; no clear superiority over MICT; generally feasible	Overlap and heterogeneity of included reviews
Castañeda-Babarro & Martinez Aguirre-Betolaza, 2026	Editorial synthesis	Resistance training in oncology	Positions resistance training as a core supportive-care modality	Not a primary study or systematic review
Beltrà et al., 2021	Focused mechanistic review; preclinical emphasis	Mitochondria and cachectic muscle	Links mitochondrial dysfunction to wasting and impaired regeneration	Limited human causal evidence
Zhang et al., 2019	Mechanistic review	Tumour physiology and immunity	Integrates perfusion, hypoxia, lactate, pH, and immune competence	Model is largely hypothesis-generating
Sidhu et al., 2025	Clinician-focused review; 11 studies	Exercise for CIPN	Multimodal, balance and sensorimotor training show promise	Small heterogeneous studies; incomplete blinding/controls
García-Chico et al., 2023	Narrative review	Exercise and breast-cancer hallmarks	Strongest synthesis for proliferation, apoptosis, immunity, inflammation	Gaps for mutation, plasticity, senescence and metastasis
Feng et al., 2024	Mini review	Broad exercise-cancer mechanisms	Integrates tumour microenvironment, cytokines and treatment effects	Broad scope and heterogeneous evidence
Li et al., 2026	Mini review	Exercise-induced myokines	IL-6, irisin, SPARC, OSM and decorin as context-dependent mediators	Predominantly preclinical; source and kinetics often unresolved
Vinolo-Gil et al., 2023	Systematic review; 5 oncology studies	Blood-flow-restriction exercise	Potential gains in function, strength, lean mass and postoperative recovery	Small evidence base, protocol variation and bias concerns
Halle et al., 2020	Mechanistic review	Exercise and cancer-induced muscle wasting	Links loading, mTORC1, redox balance and anabolic sensitivity	Insufficient clinical trials for a cachexia-specific recommendation
Brummer et al., 2023	Preclinical/clinical review	Exercise and checkpoint inhibition	Biological rationale and early evidence for immune sensitisation	Human treatment-response evidence remains insufficient
He et al., 2025	Mechanistic/translational review	Tumour-immune metabolome	Integrates AMPK-mTOR-HIF-1α, PGC-1α-ERRα and IL-6/STAT3	Candidate biomarkers remain unstandardised
Tokatlıoğlu et al., 2026	Systematic review; 3 RCTs	Wearables in breast cancer	Supports monitoring, adherence and self-management	Cannot isolate independent wearable effects
Hojman et al., 2018	Perspective	Molecular mechanisms across cancer continuum	Foundational multiscale exercise-as-cancer-medicine framework	Many mechanisms derived from animal models
Dethlefsen et al., 2017	Human serum/cell experiments + murine tumours	Catecholamine-beta-adrenergic-Hippo/YAP signalling	Exercise serum reduced cell viability; beta blockade interrupted effect	Small human serum cohorts; subtype-specific signalling
Mustian et al., 2017	Meta-analysis; 113 RCTs, 11,525 participants	Cancer-related fatigue treatments	Exercise and psychological therapies outperformed pharmaceuticals	Breast-cancer dominance and limited long-term follow-up
Betof et al., 2015	Randomised murine breast-cancer experiment	Vascularity, hypoxia and cyclophosphamide response	Vessel maturation, perfusion and chemotherapy growth-delay improved	Preclinical model; no direct human validation
Campbell et al., 2019	International multidisciplinary consensus	Exercise prescription for survivors	Avoid inactivity; outcome-specific aerobic/resistance/combined prescriptions	Evidence concentrated in early breast and prostate cancer
Pedersen et al., 2016	Mechanistic study across several mouse tumour models	Epinephrine/IL-6-dependent NK mobilisation	Causal interruption supports an NK-mediated tumour-control pathway	Animal models and voluntary running limit direct dose translation

INTEGRATED EVIDENCE SYNTHESIS

The included literature converged on a multiscale model in which exercise acts simultaneously on the patient, contracting skeletal muscle, circulating mediators, immune-cell trafficking, and the tumour microenvironment (Figure 1).

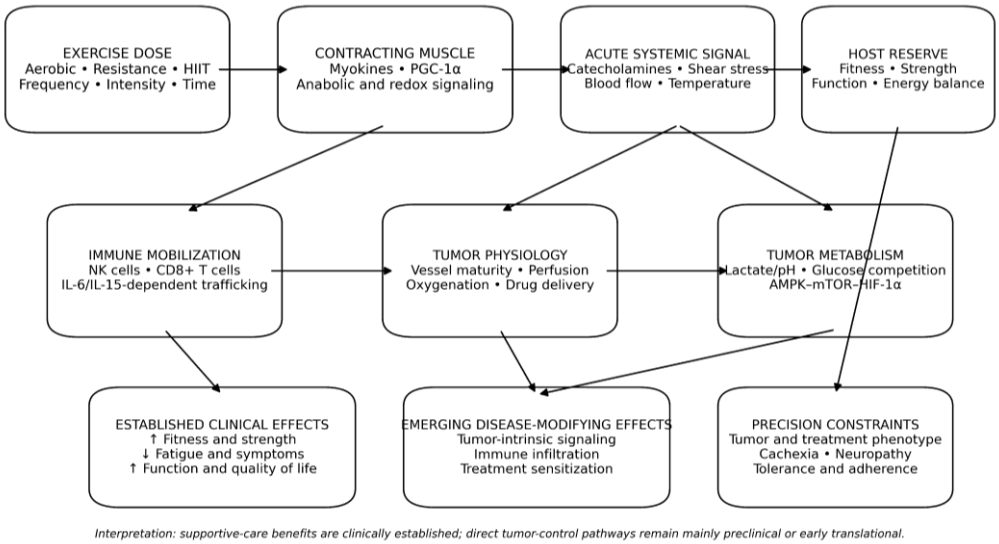

Figure 1. Multiscale model of exercise in oncology. Exercise generates integrated muscular, neuroendocrine, haemodynamic, metabolic, and immune signals. Clinical benefits for fitness, strength, fatigue, function, and quality of life are supported by mature evidence. Direct tumour control, immune sensitisation, and treatment-response effects remain predominantly preclinical or early translational. Arrows indicate proposed biological influence rather than proven clinical causality.

Acute exercise signalling: Catecholamines, Hippo-YAP, and myokines

An acute exercise bout produces a transient systemic signal characterised by increased blood flow, sympathetic activation, catecholamine release, and secretion of muscle-derived factors. Hojman et al. (2018) proposed that these physical and endocrine signals can influence tumour growth kinetics, metabolism, immunogenicity, and treatment response. Within this model, the exercise bout is not a nonspecific stressor; it is a coordinated perturbation that may repeatedly expose tumours and immune cells to short-lived biological signals.

The most direct evidence for a tumour-intrinsic pathway comes from Dethlefsen et al. (2017). Serum collected after exercise from women with breast cancer and healthy women reduced the viability of hormone-sensitive MCF-7 and hormone-insensitive MDA-MB-231 cells by 11% to 19%. Preincubation of MCF-7 cells with exercise-conditioned serum also reduced subsequent tumourigenesis by 50% in mice. Beta-adrenergic blockade abolished the suppressive response, while epinephrine and norepinephrine activated Hippo signalling, increased YAP phosphorylation and cytoplasmic retention, and reduced expression of YAP-regulated genes. Voluntary running reduced MCF-7 and MDA-MB-231 tumour growth by 36% and 66%, respectively. The pathway was more clearly demonstrated in MCF-7 cells, underscoring that tumour subtype can determine mechanistic responsiveness.

A complementary immune mechanism was demonstrated by Pedersen et al. (2016). Voluntary wheel running reduced tumour incidence and growth by more than 60% across several murine tumour models. Epinephrine mobilised natural killer cells into the circulation, and muscle-derived interleukin-6 contributed to their redistribution and intratumoral accumulation. Beta-adrenergic blockade or interleukin-6 neutralisation attenuated natural killer cell infiltration and tumour suppression. These experiments provide unusually strong causal evidence within animal models because both the mobilising signal and the cellular effector were experimentally interrupted.

Myokines extend this muscle-to-tumour and muscle-to-immune communication network. Reviews identify interleukin-6, interleukin-15, irisin, secreted protein acidic and rich in cysteine, oncostatin M, and decorin as candidate mediators of direct growth inhibition, immune-cell metabolic support, extracellular-matrix remodelling, or inflammatory regulation (Li et al., 2026). However, the direction of effect is context dependent. Transient muscle-derived interleukin-6 during exercise may support immune mobilisation and anti-inflammatory signalling, whereas chronically elevated tumour- or host-derived interleukin-6 can activate STAT3, promote immune dysfunction, and accelerate muscle wasting. Similarly, oncostatin M, secreted protein acidic and rich in cysteine, and decorin can have different effects across cancer types and biological contexts. The mechanistic signal should therefore be defined by source, duration, concentration, receptor context, and tumour phenotype rather than by cytokine name alone. Importantly, these proposed myokine-mediated antitumour effects are supported predominantly by cell and animal studies and heterogeneous early human observations; they should therefore be regarded as hypothesis-generating rather than as established mechanisms of tumour control in patients.

Tumour vascular and metabolic remodelling

Solid tumours commonly contain disorganised vessels, heterogeneous perfusion, hypoxia, glucose competition, lactate accumulation, and extracellular acidosis. These features are not passive consequences of tumour growth; they limit drug delivery, impair cytotoxic lymphocyte metabolism, favour regulatory and suppressive immune populations, and contribute to treatment resistance. Zhang et al. (2019) proposed that exercise may normalise this physiological microenvironment by improving vascular function and reducing the metabolic barriers that prevent mobilised immune cells from entering and functioning within tumours.

Betof et al. (2015) provided direct preclinical support for this proposition. In immunocompetent murine breast cancer models, voluntary exercise reduced tumour growth, increased apoptosis by approximately 1.4-fold, increased microvessel density and vessel maturity, improved perfusion, and reduced intratumoral hypoxia. Exercise combined with cyclophosphamide prolonged tumour-growth delay more than chemotherapy alone. The key interpretation is not that exercise simply stimulates angiogenesis. Rather, exercise appears capable of producing a more organised and functional vascular network, thereby improving oxygen and drug delivery. This distinction between vascular normalisation and indiscriminate vessel proliferation is central to reconciling apparently conflicting angiogenic observations.

Metabolic normalisation may be equally important. Tumour-derived lactate and low extracellular pH impair T-cell and natural killer cell cytotoxicity and create nutrient competition between malignant and immune cells. The reviewed preclinical evidence indicates that exercise can reduce tumour or circulating lactate, improve oxygen availability, and shift the tumour toward a less glycolytic environment (Zhang et al., 2019). He et al. (2025) expanded this framework to glucose, amino-acid, lipid, and mitochondrial metabolism, proposing integrated AMPK-mTOR-HIF-1α and PGC-1α-ERRα networks that connect systemic metabolic flexibility with immune-cell fitness. This is biologically coherent, but many specific pathway claims remain derived from heterogeneous preclinical studies and should not yet be interpreted as validated clinical biomarkers.

The broader breast cancer hallmark literature supports effects on proliferation, growth suppression, apoptosis, inflammation, immune evasion, and metabolic regulation, while identifying major gaps for genome instability, phenotypic plasticity, senescence, and some aspects of metastasis (García-Chico et al., 2023). Thus, exercise may influence several cancer hallmarks, but the depth of evidence differs sharply across hallmarks and remains dominated by aerobic preclinical models.

Immune mobilisation and the immunotherapy hypothesis

Exercise-induced leucocytosis and redistribution preferentially mobilise cytotoxic cell populations, including natural killer cells and effector T cells. Improved tumour perfusion, endothelial adhesion, reduced hypoxia, and lower metabolic suppression may then determine whether circulating cells can enter the tumour and retain function. This two-stage model—systemic mobilisation followed by tumour access and metabolic competence—helps explain why measuring blood immune cells alone may be insufficient.

Brummer et al. (2023) reviewed the possibility that exercise could enhance immune checkpoint inhibition by shifting the tumour microenvironment from a suppressive toward an inflamed phenotype. The preclinical findings are promising but inconsistent. In a melanoma model, exercise alone markedly reduced tumour growth and did not add to anti-PD-1 or anti-PD-L1 therapy, possibly because the independent exercise effect was already large. In a pancreatic adenocarcinoma model that was resistant to anti-PD-1 monotherapy, exercise increased cytotoxic T-cell infiltration and sensitised the tumour to checkpoint blockade. Early human studies have reported higher intratumoral CD8-positive T-cell abundance after preoperative exercise in pancreatic cancer and a dose-related signal for natural killer cell infiltration after preoperative high-intensity interval training in prostate cancer, but clinical response and survival data remain insufficient. Thus, the available evidence does not establish that exercise improves checkpoint-inhibitor efficacy in humans, and mechanistic signals should not be interpreted as evidence of improved clinical response or survival.

Accordingly, exercise-immunotherapy synergy is a plausible, testable hypothesis rather than an established treatment effect. Tumour immune sensitivity, baseline infiltration, treatment timing, exercise dose, and the magnitude of the exercise-alone response may determine whether additivity, synergy, or no interaction is observed. Trials should therefore be designed around mechanistically selected tumours and should measure intratumoral immune composition, metabolic state, treatment response, and patient-centred outcomes in parallel.

Skeletal muscle, mitochondria, and cancer cachexia

Exercise also acts on the host tissues that determine treatment tolerance and functional reserve. Cancer cachexia combines inflammation, altered energy metabolism, anorexia or malnutrition in some patients, endocrine disruption, reduced activity, mitochondrial dysfunction, impaired regeneration, hypercatabolism, and resistance to anabolic stimuli. Mitochondrial abnormalities can precede overt muscle wasting, and chemotherapy may further impair oxidative capacity and muscle regeneration (Beltrà et al., 2021).

Halle et al. (2020) described a mechanistic rationale for exercise in cachexia through improved insulin sensitivity, antioxidant capacity, mitochondrial biogenesis, neuromuscular loading, suppression of proteolytic signalling, and activation of protein synthesis through the IGF-1-PI3K-Akt-mTORC1 axis. Preclinical studies suggest that resistance-type loading, electrical stimulation, eccentric contractions, and moderate aerobic exercise can preserve muscle function or metabolic quality, but responses are variable and often depend on intervention timing. Exercise performed before severe wasting may be more effective than attempting to reverse advanced cachexia.

The same biology creates a safety tension. Exercise can restore anabolic sensitivity and preserve function, yet excessive whole-body energy expenditure may worsen negative energy balance in a severely cachectic patient. Neither the cachexia review nor current clinical evidence supports a universal exercise prescription for this population. A multimodal strategy combining carefully dosed resistance or functional training with nutritional and medical management is more defensible than exercise alone. Low-load blood-flow-restriction training is conceptually attractive when heavy loading is not tolerated. A systematic review of five oncology

studies reported improvements in physical function, strength, lean mass, quality of life, and some postoperative outcomes without an observed increase in serious complications; however, the small and heterogeneous evidence base, variable protocols, and risk-of-bias concerns preclude routine use without specialist supervision (Vinolo-Gil et al., 2023).

Clinical effectiveness and modality-specific evidence

Clinical evidence is most consistent for fitness, strength, function, fatigue, and quality of life. In 14 studies of breast cancer survivors, concurrent aerobic and resistance training produced improvements in body mass, muscular strength, and maximal oxygen uptake, while percentage fat mass did not change significantly. Reported pooled effects included a body-mass difference of -2.23, a strength difference of 4.93, and a maximal oxygen-uptake difference of 3.03 in the original measurement scales used by the meta-analysis; the borderline confidence interval for body mass index and the heterogeneity of intervention reporting warrant cautious interpretation (Madeira et al., 2025). The review emphasised that duration, frequency, intensity, and individualisation modified outcomes.

For high-intensity interval training, an umbrella review of seven systematic reviews found a small improvement in cardiorespiratory fitness compared with non-HIIT additions to cancer care (standardised mean difference 0.45, 95% confidence interval 0.24 to 0.65), but no significant advantage over moderate-intensity continuous training (standardised mean difference 0.23, 95% confidence interval -0.04 to 0.50). Adherence ranged from 54% to 100%, and adverse events were generally absent or mild (Herranz-Gómez et al., 2022). HIIT is therefore a time-efficient option for selected patients, not evidence that maximal intensity is universally superior.

Fatigue provides the clearest example of exercise as a clinical treatment. Mustian et al. (2017) synthesised 113 randomised trials including 11,525 participants. Exercise reduced cancer-related fatigue with a weighted effect size of 0.30, psychological interventions with 0.27, and combined exercise-psychological interventions with 0.26, whereas pharmacological interventions produced a smaller effect of 0.09. Exercise and psychological interventions were significantly more effective than the available pharmaceutical approaches. Exercise mode did not materially change the fatigue response, but treatment phase and delivery format influenced effectiveness.

Symptom-specific prescription is also emerging. A review of 11 studies in chemotherapy-induced peripheral neuropathy found that multimodal interventions incorporating aerobic, resistance, balance, sensorimotor, or yoga elements were associated with improvements in symptom severity, function, and quality of life (Sidhu et al., 2025). The evidence was limited by small samples, inconsistent controls and blinding, and heterogeneous prescriptions. Clinically, balance and sensorimotor components, lower starting intensity, progressive loading, fall-risk management, and referral to an exercise or rehabilitation professional are more defensible than a generic aerobic-only programme.

Wearable technologies may improve implementation rather than act as independent therapies. A systematic review identified only three randomised trials in breast cancer, involving activity trackers, smart bracelets, or an electroencephalography headband. Wearable-supported interventions increased moderate-to-vigorous activity, and one device-guided aerobic programme during chemotherapy improved peak oxygen uptake by 2.43 mL/kg/min, handgrip strength by 7.10 kg, fatigue, sleep, anxiety, and depression, with mean adherence of 81.8% and no serious exercise-related adverse events (Tokatlıoğlu et al., 2026). The devices primarily enabled monitoring, feedback, and adherence; the therapeutic content remained exercise or mindfulness.

DISCUSSION

The evidence reveals a two-track translational architecture. Track one is clinically mature: exercise reliably improves functional and patient-reported outcomes, particularly cardiorespiratory fitness, strength, fatigue, physical function, and quality of life. Track two is mechanistically rich but clinically immature: exercise may suppress tumour-intrinsic signalling, normalise tumour physiology, reprogramme immunometabolism, increase immune infiltration, and improve treatment sensitivity. The strongest causal evidence in track two comes from controlled animal and cell experiments, while direct confirmation in human tumours remains sparse.

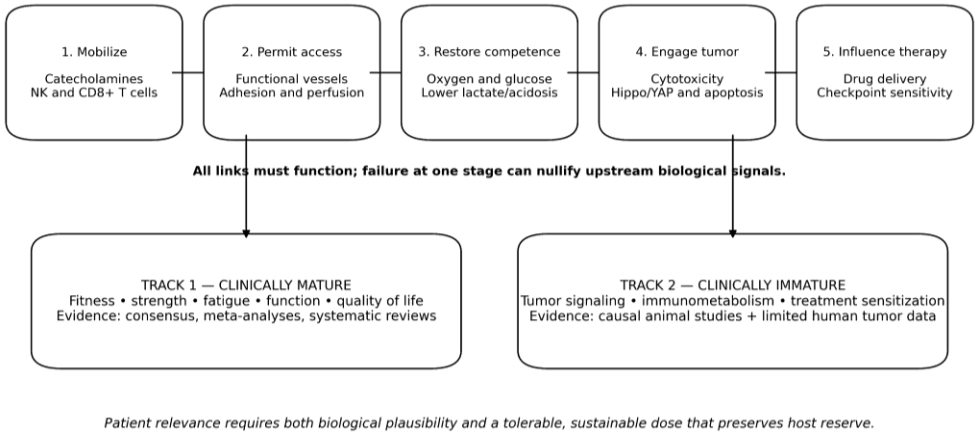

Figure 2. Dependency chain and evidence maturity. Exercise-mediated tumour control requires successful immune mobilisation, tumour access, metabolic competence, tumour engagement, and interaction with treatment. The lower panels distinguish clinically mature supportive-care outcomes from mechanistically rich but clinically immature disease-modifying hypotheses.

Table 2. Mechanistic domains, evidence maturity, and translational gaps.

Mechanistic domain	Proposed biological route	Primary supporting evidence	Evidence maturity	Priority gap
Catecholamine-beta-adrenergic-Hippo/YAP	Acute exercise raises epinephrine/norepinephrine; beta-adrenergic signalling promotes YAP phosphorylation and cytoplasmic retention	Exercise-conditioned human serum, breast-cancer cell lines, murine xenografts	Early translational	Confirm physiological exposure, subtype specificity and in-human tumour signalling
Epinephrine/IL-6-NK-cell axis	Epinephrine mobilises NK cells; muscle-derived IL-6 supports redistribution and tumour infiltration	Causal blockade and cell-depletion experiments in multiple mouse models	Strong preclinical	Validate intratumoral trafficking and clinical outcomes in humans
Vascular normalisation	Exercise improves vessel maturity, perfusion and oxygenation, potentially increasing immune access and drug delivery	Immunocompetent murine breast-cancer model; mechanistic reviews	Strong preclinical	Distinguish durable normalisation from angiogenesis in human tumours
Lactate, acidity and substrate competition	Reduced hypoxia/glycolysis may lower lactate and restore T/NK-cell metabolism	Preclinical tumour and immune-metabolism studies; integrative reviews	Predominantly preclinical	Standardise tumour metabolite and pH measurements around exercise
Checkpoint-inhibitor sensitisation	Exercise may convert suppressive tumours through T-cell infiltration, perfusion and metabolic support	Mixed murine results; early preoperative human biopsy studies	Emerging	Test tumour-selected populations with response and survival endpoints
Myokine signalling	IL-6, IL-15, irisin, SPARC, OSM and decorin may act directly on tumours or indirectly through immunity/ECM	Cell/animal studies and heterogeneous small human studies	Hypothesis-rich	Resolve source, dose, timing, receptor context and cancer specificity
Cachexia/mitochondrial-anabolic rescue	Loading and aerobic adaptation may improve PGC-1α signalling, redox homeostasis and mTORC1-dependent synthesis	Mechanistic reviews and mostly preclinical interventions	Early translational	Determine timing, energy balance, nutrition interaction and tolerable dose

This distinction resolves an important conceptual problem. Exercise does not need to shrink tumours directly to be medically valuable; improving physiological reserve, reducing fatigue, preserving muscle, and enabling treatment completion are substantial therapeutic outcomes. Conversely, the supportive-care evidence should not be used to imply proven effects on recurrence, progression, or immunotherapy response. The appropriate interpretation is that exercise is established supportive therapy with plausible disease-modifying potential.

The mechanistic domains are also interdependent rather than additive. Catecholamine-driven immune mobilisation will be ineffective if abnormal vasculature prevents extravasation. Improved perfusion will not restore cytotoxicity if lactate and nutrient competition remain suppressive. A favourable tumour response may still be clinically irrelevant if the prescribed dose accelerates weight loss or cannot be sustained. Figure 2 depicts this dependency structure.

Contradictions and boundary conditions

Several apparent contradictions require explicit interpretation. First, interleukin-6 is both a candidate antitumour myokine and a driver of cachexia and tumour-promoting inflammation. The distinction lies in source and kinetics: a transient muscle-derived pulse during exercise is biologically different from chronic systemic or intratumoral elevation. Second, increased microvessel density may appear proangiogenic, yet the Betof model showed greater vessel maturity, perfusion, apoptosis, and chemotherapy response, supporting functional normalisation rather than uncontrolled angiogenesis.

Third, intensity is not a linear determinant of benefit. HIIT improves fitness and is generally feasible, but it has not clearly outperformed moderate continuous training. Acute immune-cell mobilisation increases with intensity, whereas exhaustive or poorly tolerated exercise may impair adherence, recovery, or energy balance. The optimal dose is therefore outcome-specific: the intensity that maximises peak oxygen uptake may not be the intensity that best preserves muscle in cachexia or minimises falls in neuropathy.

Fourth, the myokine and checkpoint literatures are susceptible to mechanistic overreach. Many candidate pathways are based on isolated models, supraphysiological exposures, or indirect associations. Li et al. (2026) and Feng et al. (2024) both emphasised heterogeneity and context dependence, while He et al. (2025) proposed multiple candidate biomarkers that remain unstandardised. Mechanistic plausibility should guide trial design, not substitute for clinical validation.

A further limitation concerns the structure of the evidence base itself. A substantial proportion of the included literature consists of systematic or narrative reviews, umbrella reviews, perspectives, editorials, and mechanistic syntheses rather than primary prospective clinical trials. Consequently, some mechanistic domains are represented through overlapping secondary interpretations of a comparatively smaller body of primary evidence. This structure is appropriate for a focused integrative mini review, but it limits causal inference, may amplify publication or citation biases present in the underlying literature, and precludes firm conclusions regarding tumour response, recurrence, survival, or treatment sensitisation. The mechanistic frameworks proposed here should therefore be interpreted as evidence-informed models for hypothesis generation and trial design rather than as clinically validated antitumour effects.

Clinical and practical implications

A practical prescription should begin with the desired outcome rather than a universal weekly dose. Aerobic or interval training is appropriate when cardiorespiratory deconditioning is dominant; resistance training is required when weakness, sarcopenia, or functional decline is central; and combined training is efficient when

both domains are impaired. For cancer-related fatigue, either aerobic or resistance-based exercise can be used, with modality selected according to preference, symptoms, access, and treatment constraints.

Risk-adapted modification is essential. Patients with chemotherapy-induced peripheral neuropathy need balance and sensorimotor work, fall-risk screening, and progressive exposure. Patients with severe cachexia require protection of energy balance, low-volume resistance or functional loading, and concurrent nutritional management. Blood-flow-restriction exercise should be reserved for appropriately screened patients under specialist supervision until larger safety and dose-response studies are available. HIIT should be offered to clinically stable patients who tolerate high-intensity work, not treated as a default protocol.

Implementation should use the FITT framework—frequency, intensity, time, and type—within a feedback loop. Symptoms, treatment toxicities, body mass, performance, recovery, and adherence should be monitored and the dose adjusted. Wearable devices can support this loop by providing activity, heart-rate, and adherence data, but they cannot replace clinical judgement or validated outcome assessment (Figure 3).

Table 3. Outcome-oriented exercise prescription framework derived from the included sources.

Clinical problem / goal	Primary exercise approach	Monitoring priorities	Critical implementation note
Cardiorespiratory deconditioning	Aerobic continuous or HIIT	VO_{2peak}/VO_{2max}, symptoms, recovery, adherence	HIIT is time-efficient but not clearly superior to MICT; select by tolerance
Weakness, sarcopenia, functional decline	Progressive resistance; combined training when fitness is also impaired	Strength, physical function, lean mass, fatigue	Supervise and individualise load, volume and progression
Cancer-related fatigue	Aerobic, resistance or combined exercise	Validated fatigue scale, sleep, activity, treatment phase	Exercise is a first-line nonpharmacologic option; preference can guide mode
Chemotherapy-induced peripheral neuropathy	Multimodal programme with balance and sensorimotor emphasis	Symptoms, gait, balance, falls, function, QoL	Start lower, progress by response, use aids/supervision when fall risk is high
Severe deconditioning or cachexia risk	Low-volume resistance/functional loading plus nutrition and medical care	Body mass trajectory, intake, strength, fatigue, recovery	Protect energy balance; avoid indiscriminate high-volume whole-body exercise
Inability to tolerate heavy loading	Low-load BFR only after screening and with specialist oversight	Haemodynamic response, pain, adverse events, strength/function	Promising but evidence remains small and heterogeneous
Adherence and remote delivery barriers	Wearable-supported exercise or counselling	Activity, heart rate, session completion, symptom alerts	Wearables support monitoring and feedback; they are not standalone therapy
Routine survivorship	Outcome-specific aerobic + resistance framework	Fitness, strength, fatigue, mental health, QoL	Avoid inactivity; modify dose for treatment effects and comorbidity

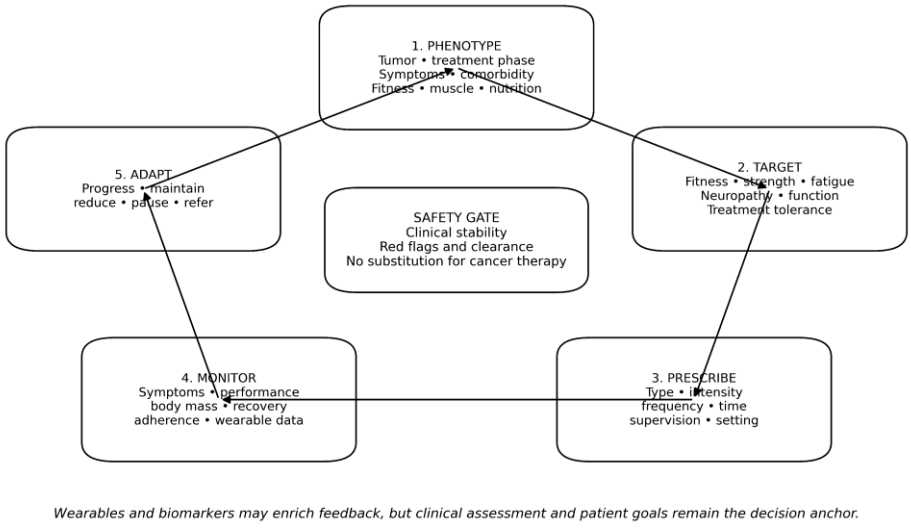

Figure 3. Closed-loop precision exercise oncology. Prescription begins with clinical and tumour phenotype, identifies the priority outcome, applies an individualised FITT dose, monitors response, and adapts the

programme. A safety gate operates throughout. Wearable and biomarker data may enrich monitoring but do not replace clinical judgement.

Future research directions

Future trials should connect tumour and host outcomes within the same protocol. Serial blood sampling, tumour biopsies when clinically feasible, imaging of perfusion and hypoxia, immune profiling, metabolomics, and functional outcomes should be aligned to the timing of exercise bouts and treatment cycles.

Dose-response trials should directly compare exercise intensity, modality, frequency, supervision, and timing. The field needs to identify the minimum effective dose for frail patients and the upper tolerable dose for fit patients, rather than extrapolating one prescription across the cancer continuum.

Mechanistic studies should distinguish acute from chronic signalling and identify cellular sources. Interleukin-6, lactate, catecholamines, and other candidate mediators should be interpreted according to tissue origin, concentration, temporal profile, receptor expression, and tumour subtype.

Immunotherapy trials should enrol biologically selected populations and evaluate whether exercise converts immune-cold tumours, improves checkpoint-inhibitor response, or merely improves fitness and tolerance. Negative and null interactions must be reported to prevent selective enthusiasm.

Finally, precision exercise oncology requires pragmatic validation. Biomarker panels and wearable data should be tested for their ability to improve decisions beyond simple clinical measures. Algorithms must remain interpretable, equitable, and clinically actionable, and should be evaluated against outcomes that matter to patients: symptoms, function, treatment completion, hospitalisation, progression, and survival.

CONCLUSIONS

Exercise has a dual identity in oncology. It is already an evidence-based supportive therapy for fitness, strength, fatigue, function, and quality of life, and it is simultaneously an emerging biological modifier of endocrine signalling, immune trafficking, tumour perfusion, metabolism, and skeletal-muscle homeostasis.

The first identity is ready for routine implementation; the second requires disciplined translation. The most defensible strategy is precision exercise prescription that protects patient reserve, targets the dominant clinical problem, and embeds mechanistic measurement within oncology trials. Exercise complements—but does not replace—anticancer treatment.

AUTHOR CONTRIBUTIONS

All authors meet the criteria for authorship in accordance with established ethical guidelines. Contributions are specified according to the CRediT (Contributor Roles Taxonomy) as follows:

Conceptualisation: Ivana Grle, Bozenka Galic Tiric.
Methodology: Maki Grle, Boriss Bazanov, Ernest Šabić.
Formal analysis: Jerko Prlić, Mate Vukoja, Goran Spaleta.
Investigation: Maki Grle, Natalija Kurtović, Davor Ljesević.
Data curation: Ivana Grle, Dejan Tiric, Naim Ćeleš.
Writing – original draft: Jerko Prlić, Dejan Tiric, Nijaz Skender, Ivan Đuroci, Patricia Zupanc.

Writing – review & editing: Ivana Grle, Dejan Tiric, Ivan Đuroci, Goran Sporiš, Besim Morina.
Supervision: Maki Grle, Jasmin Budimlić, Ivica Franjko, Ahmet Naci Dilek, Adem Preljević.

All authors have critically reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

FUNDING

Individuals who contributed to the research through support, acknowledgements, funding, and donations: Vjekoslav Radovčić, Željko Kovačević, Adnan Mustedanagić, Štefan Modrić, Ivan Stevura, Josip Lepeš, Igor Sabo, Ivan Đuroci, Miloš Maravić, Marko Žigman, Miloš Stojković, Željko Širić, Agim Hasani, Darko Dumančić, Stjepan Babić, Robert Citozi, Jakov Gogić, Veljko Vukičević, Marin Nikolić, Mario Anić Kremić, Krešimir Maronić, Tomislav Brlečić, Dino Kluk, Davor Lješević, Dominik Pick, Mladen Muškovac, Deni Hajdarović, Josip Zornjak, Štefan Modrić, Karlo Zornjak, Željko Ostrman, Baltazar Bogulin, Marijan Spehnjak, Baltazar Bogulin, Nijaz Skender, Perica Vidak, Marko Žigman, Krševan Santini, Željko Širić, Goran Špaleta, Darko Dumančić, Damir Benedeković, Robert Citozi, Dominik Mohorocić, Veljko Vukičević, Goran Vučković, Mario Anić Kremić, Nic Jamec, Tomislav Brlečić, Besim Morina, Davor Lješević, Bojan Šestan, Mladen Muškovac, Mladen Muškovac, Josip Zornjak, Hrvoje Ajman, Karlo Zornjak, Ivana Grle, Baltazar Bogulin, Maki Grle, Zoran Bogulin, Jerko Prlić, Perica Vidak, Dejan Tiric, Krševan Santini, Bozenka Galic Tiric, Goran Špaleta, Vedran Režić, Lazar Zaknić, Jose Antonio Perez Turpin, Damir Benedeković, Boriss Bazanov, Dominik Mohorocić, Davor Bučević, Bojan Šestan, Sandra Kerim, Jakov Gogić, Marko Čurković, Deni Hajdarović, Haris Čoćić, Marin Nikolić, Ivan Žižić, Hrvoje Ajman, Zlatko Triplat, Mate Vukoja, Robet Čović, Zvezdan Stefanović, Josip Zekić, Faisal Osama Mohamed Hasan Mohamed, Tomas Marczinka, Ahmed Kamal Ahmed Hasan Ali, Juraj Govorčin, Ivan Pavić, Vatroslav Horvat, Andrej Radić, Anto Aračić, Dino Bartoluci, Jasmin Ičanović, Milan Milošević, Vlatka Tomić, Dalija Kuvačić, Petra Špaleta, Vid Kučko, Miroslav Hrženjak, Goran Jelaska, Srđan Prodanović, Peruško Manuel, Šutić Danijel, Vlašić Jan, Petra Mandić, Damir Jurko, Ante Vukoja, Mauro Carvalho, Tomislav Lopac, Haris Alić, Ahmed Kamal, Marijan Jozić, Marko Erceg, Ahmet Naci Dilek, Gaetano Raiola, Deniss Dunik, Fjodor Dunik, Ilja Jazev, Mindaugas Balčiūnas, Arūnas Emeljanovas, Brigita Miežiene, Balčiuniene Vaiva, Tolga Tek, Perez Aleixandre Pablo, Sport Sapiens OU.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

AI USE DISCLOSURE

Artificial intelligence (AI) tools were used to assist with translation, language editing, clarity, and readability. The authors confirm that they have independently reviewed and verified the scientific content, methodological descriptions, references, tables, data interpretation, and conclusions. The authors take full responsibility for the accuracy, integrity, originality, and accountability of the manuscript.

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