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RESEARCH

Physical activity and systemic treatment outcomes in advanced thyroid cancer

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Abstract

Introduction: Physical activity interventions could play a critical role in tolerance and outcome during anti-neoplastic therapy.

Aim: This study aims to evaluate the role of physical activity and its maintenance on treatment safety and efficacy in patients with advanced thyroid cancer.

Methods: We enrolled 28 patients with advanced thyroid cancer, treated with kinase inhibitor therapy for a median follow-up of 26 months. Three modified long-form International Physical Activity Questionnaires were administered before treatment, at an intermediate follow-up point and at the last follow-up point. Metabolic equivalents were calculated at each time point. Tumour response was evaluated according to RECIST, version 1.1.

Results: Patients inactive at baseline experienced more treatment interruptions during both the first (85 vs 30%, $P = 0.01$) and second half of the follow-up period (85 vs 47%, $P = 0.08$) and had more frequently a progressive disease (42 vs 14%, $P = 0.15$), compared to those who were mildly or highly active. Patients who declined their physical activity during treatment had more treatment interruptions (100 vs 31%, $P = 0.006$), more adverse events considering both the number (>5) and the grade (≥3) (100 vs 31%, $P = 0.006$ and 100 vs 38%, $P = 0.01$), more hospitalization due to toxicities (66 vs 8%, $P = 0.008$) and a more progressive disease (40 vs 8%, $P = 0.09$). The number of toxicities was inversely correlated with metabolic equivalents lost ($r = -0.15$, $P = 0.04$).

Conclusion: This is the first study showing that maintaining adequate physical activity levels is associated with better treatment tolerance and outcomes in advanced thyroid cancer patients on kinase inhibitor therapy, supporting the need for prospective prehabilitation trials.

Keywords: thyroid cancer; physical activity; prehabilitation; kinase inhibitor therapy

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Introduction

Patients with progressive radioiodine-refractory differentiated thyroid cancer (RAI-R DTC) and advanced medullary thyroid cancer (MTC) have a poor overall survival (10 year-specific OS ~ 10%) (1, 2). Over the past decade, kinase inhibitor (KI) therapy with multikinase inhibitors (MKIs) and target therapies have significantly changed the course of these diseases, by effectively prolonging progression-free survival (PFS) (3). In Europe, the MKIs sorafenib, lenvatinib (LEN) and cabozantinib (CABO) are approved for RAI-R DTC, vandetanib (VAN) and CABO for MTC, and the gene-targeted selpercatinib (SELP) and larotrectinib for cancers harbouring rearranged during transfection (RET) proto-oncogene alterations and neurotrophic tyrosine receptor kinase (NTRK) fusions, respectively (4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14). The efficacy of these drugs is accompanied by a variable incidence of adverse events (AEs), particularly for MKI treatment. These AEs can significantly impact patients' quality of life (QoL) and often lead to treatment reductions or discontinuations, with potential negative implications for prognosis (15). Fatigue, weight loss and anorexia are challenging-to-manage AEs and frequently result in muscle mass loss, being cachexia and sarcopenia observed in some patients (16, 17). By contrast, newly developed targeted therapies (e.g., SELP) exhibit more selective mechanisms of action and therefore constitute a valuable therapeutic option associated with a reduced burden of AEs.

In other cancer types and treatment settings, prehabilitation programmes are becoming common clinical practice. Prehabilitation relies on multimodal, patient-tailored interventions before cancer treatment, aimed at optimizing physical and psychological health to improve treatment outcomes and tolerability. Prehabilitation has proven to be effective in improving treatment tolerance and reducing AEs, ultimately offering prognostic benefits (18, 19). Within multimodal prehabilitation programmes, physical activity interventions are particularly important, helping to reduce sarcopenia and improve cardiometabolic resilience.

In the context of thyroid cancer (TC) patients treated with KIs, the prehabilitation concept is gaining increasing recognition, as highlighted by a recent narrative review from experts in the field (20), in which its application is supported and encouraged, but to date, no real-life data are available on the role of physical activity (PhysA) in series of thyroid cancer patients. This study, therefore, aims to retrospectively evaluate the role of basal PhysA and its maintenance on treatment outcomes in a single-centre cohort of TC patients on KIs.

Methods

Patients

This study was conducted in accordance with the ethical standards of the institutional research committee and with the 2024 Declaration of Helsinki (21). All patients were enrolled in a protocol approved by the Ethical Committee of the Istituto Auxologico Italiano (study approval code: 2022_03_08_03) and provided written informed consent for the use of anonymized clinical data for research purposes. A total of 28 consecutive patients (12 F and 16 M; mean age at diagnosis 52.7 years) with advanced RAI-R DTC and MTC were retrospectively included (Supplemental Table 1 (see section on Supplementary materials given at the end of the article)). Patients were, at the time of the analysis, on treatment with lenvatinib (LEN; n = 18), vandetanib (VAN; n = 4), cabozantinib (CABO; n = 4) or selpercatinib (SELP; n = 2) at a single tertiary referral centre and followed up for a median period of 26 months. Of these, 25 patients (89.3%) were on first-line treatment, while 3 patients (10.7%) received second-line treatment: one MTC patient treated with SELP had previously received CABO, and two patients treated with CABO had previously been treated with LEN.

The baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (n = 12) or 1 (n = 16). Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. For each patient, the worst CTCAE grade experienced during the follow-up (FU) was recorded. Levothyroxine dosage was titrated in patients with RAI-R DTC to keep serum thyroid-stimulating hormone (TSH) levels below the normal range (target: 0.01–0.1 mU/L), both before and during antineoplastic treatment. For patients with advanced MTC, TSH levels were maintained within the normal range (0.5–2 mU/L).

Tumour response was assessed by whole-body computed tomography (CT) and/or ^{18}F-fluorodeoxyglucose (FDG) or ^{18}F-dihydroxyphenylalanine (DOPA) positron emission tomography/computed tomography (PET/CT). The best morphological response (BMR) was evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1 (22).

Physical activity evaluation

A sports science specialist (FC) designed a structured questionnaire to evaluate patients' PhysA levels. The questionnaire was based on the validated International Physical Activity Questionnaire (IPAQ), which quantifies frequency, duration and intensity of activity across various domains (23). Although originally validated for populations aged 15–69, the IPAQ can also be applied to older adults with minor adaptations (24).

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For this reason, we utilized a modified short-form IPAQ tailored to include typical daily activities of elderly patients (Supplemental Table 2). To further refine the measurement of exercise intensity, each activity was assessed using the Borg Rating of Perceived Exertion (6–20 scale), a subjective metric of effort perceived by the individual during physical exertion (25).

The questionnaire was administered retrospectively, referring to the following three time points:

- T0: baseline, before KI initiation.
- T1: intermediate FU (median: 13 months; range: 6–96 months). T1 was assessed as the midpoint of the treatment period.
- T2: final FU (median: 26 months; range: 12–192 months; T2 data unavailable for two patients).

For each activity, metabolic equivalents (METs) were calculated, enabling a reliable estimation of weekly energy expenditure per time point (23). Based on their MET values and physical activity profiles, patients were classified into three categories:

- Inactive: no reported activity, or activity insufficient to meet minimum criteria.
- Mildly active: meeting at least one of the following:
  - ≥3 days of vigorous activity ≥20 min/day,
  - ≥5 days of moderate activity ≥30 min/day, and
  - ≥5 days of any activity accumulating ≥600 MET-min/week.
- Highly active: meeting at least one of the following:
  - ≥3 days of vigorous activity totalling ≥1,500 MET-min/week and
  - ≥7 days of any activity accumulating ≥3,000 MET-min/week.

To note, no specific physical activity programme was implemented during the study and, as in routine clinical practice, patients were generally advised to maintain a healthy and active lifestyle.

Furthermore, no additional clinical features or comorbidities were identified that could account for the baseline PhysA status observed in inactive patients.

Statistical analysis

Quantitative variables were expressed as mean ± standard deviation (SD) or median with range, depending on the normality of distribution (assessed using the Shapiro–Wilk test). Categorical variables were presented as absolute frequencies and percentages.

Between-group comparisons for continuous variables were conducted using either the Student *t*-test (parametric data) or the Mann–Whitney U test (non-parametric data). Categorical variables were compared using the chi-square (χ^2) test or Fisher's exact test, as appropriate.

Correlations between continuous variables were evaluated using Pearson's correlation coefficient (parametric data) or Spearman's rank correlation (non-parametric data). PFS was analysed using the Kaplan–Meier method, and survival curves were compared using the log-rank test. A P-value <0.05 was considered statistically significant.

All statistical analyses were performed using MedCalc statistical software, version 19.2.0 (MedCalc Software bvba, Belgium).

Results

Baseline and longitudinal assessment of physical activity

At baseline (T0), 7/28 patients (25%) were classified as physically inactive according to their weekly METs,

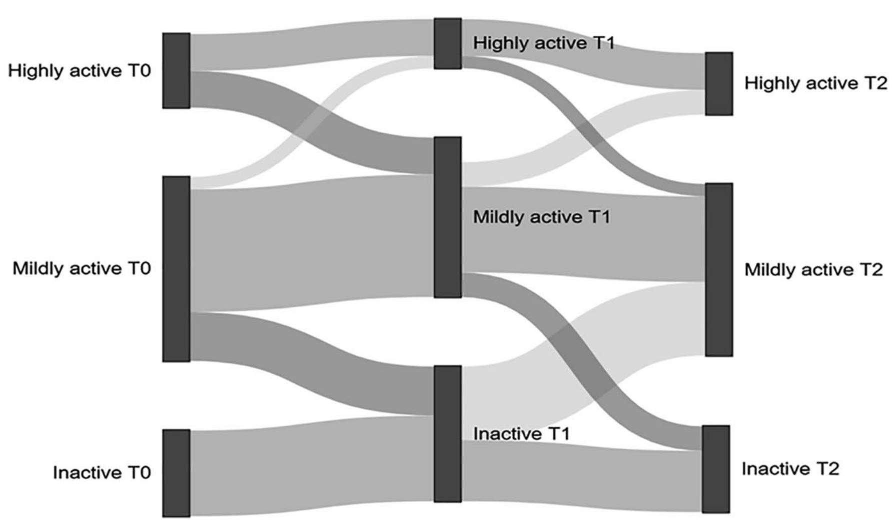

Figure 1

Sankey diagram of the physical activity status variation during the follow-up (FU) at three points of analysis (T0, T1 and T2). At the end of the FU, 29% of the highly active patients at T0 and 27% of the mildly active patients at T0 worsened their physical activity status; moreover, 43% of the inactive patients at T0 remained inactive at the end of the FU.

Table 1 Correlation between basal physical activity status and safety/efficacy of kinase inhibitor therapy at T1 and T2.

	Evaluation at T1			Evaluation at T2		
Variables	**Inactive (*n* = 7)**	**Mildly and highly active (*n* = 20)**	***P***	**Inactive (*n* = 7)**	**Mildly and highly active (*n* = 21)**	***P***
KI dose reduction	4 (57%)	9 (45%)	0.58	4 (57%)	10 (47%)	0.66
KI interruption	6 (85%)	6 (30%)	0.01	6 (85%)	10 (47%)	0.08
>3 AEs	4* (100%)	13 (65%)	0.24	6 (85%)	15 (71%)	0.45
>4 AEs	4* (100%)	12 (60%)	0.15	6 (85%)	13 (61%)	0.25
>5 AEs	3* (75%)	9 (45%)	0.37	4 (57%)	10 (47%)	0.66
1 AE Gr. ≥ 3	4* (100%)	8 (40%)	0.37	4 (57%)	13 (61%)	0.82
PD during FU	3 (42%)	2 (10%)	0.05	3 (42%)	3 (14%)	0.15

KI, kinase inhibitor; T1, intermediate time on analysis; T2, last time of analysis; AEs, adverse events; Gr., grade; PD, progressive disease; and FU, follow-up. Adverse event grade was assessed according to CTCAE, version 5.0; tumour response was assessed according to RECIST criteria, version 1.1.
*Data missing for three patients.

without other known interfering comorbidities. Of these, 3 (43%) remained inactive throughout the FU period. Among the 21 patients who were either mildly or highly active at baseline, 7 (33%) experienced a decline in physical activity status by the final assessment (T2) (Fig. 1). In particular, five mildly active and two highly active patients at T0 dropped their status during the FU. Conversely, two patients experienced a temporary decline at the intermediate time point (T1) but regained their original PhysA status by T2. As a whole, during KI therapy, a decline in physical activity levels was observed in 16 out of 28 patients (57%). No differences were observed between patients declining and not declining their PhysA in terms of sex (10/16 M vs 6/12 F, $P = 0.5$) and age (64 vs 58.9 years, $P = 0.44$) (data not shown). This reduction was distributed across treatment subgroups as follows: 11/18 (61%) receiving LEN, 2/4 (50%) receiving VAN, 2/4 (50%) receiving CABO and 1/2 (50%) receiving SELP. On the other hand, five patients demonstrated an improvement in PhysA levels during treatment: four who were inactive at T0 and 1 was mildly active (2 LEN, 2 VAN and 1 CABO) (Fig. 1).

Impact of baseline physical activity on treatment tolerability and disease progression

Inactive patients at baseline presented a similar initial KI choice compared with mildly and highly active patients (MKI treatment in 7/7 vs 19/21, $P = 0.4$), and the three patients on second-line treatment were mildly and highly active at baseline. Moreover, the FU time from treatment start was not statistically different for inactive patients compared with mildly and highly active patients ($P = 0.1$)

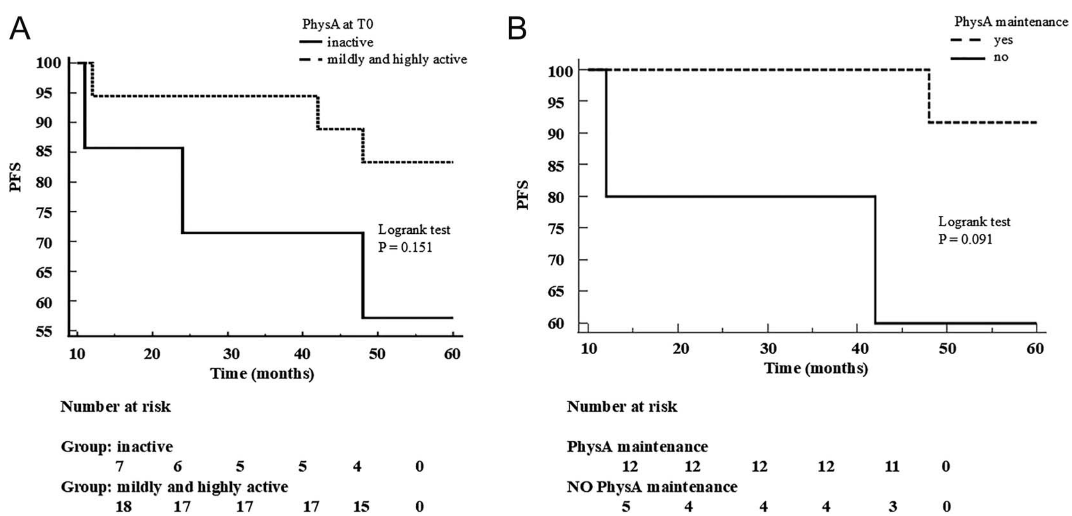

Figure 2

(A) Kaplan–Meier analysis of basal physical activity (PhysA) status and PFS: inactive vs mildly and highly active patients at T0. Considering their basal PhysA status (at T0), inactive patients showed, though not significantly, a worse PFS (57%) than mildly active patients (84%) and highly active patients (80%) during the entire follow-up (FU) ($P = 0.351$). (B) Kaplan–Meier analysis of PhysA maintenance and PFS. Dividing patients according to their PhysA status maintenance during the follow-up (FU) (no vs yes), patients who did not maintain and who worsened their PhysA status showed a worse PFS (60%) than patients who maintained it (92%) (P 0.091).

Table 2 Correlation between physical activity maintenance and kinase inhibitor safety/efficacy.

Variables	PhysA maintenance (*n* = 13)	PhysA decline (*n* = 6)	*P*
KI dose reduction	5 (38%)	5 (83%)	0.07
KI dose interruption	4 (31%)	6 (100%)	0.006
>3 AEs	8 (62%)	6 (100%)	0.08
>4 AEs	6 (46%)	6 (100%)	0.02
>5 AEs	4 (31%)	6 (100%)	0.006
1 AE Gr. ≥ 3	5 (38%)	6 (100%)	0.01
2 AE Gr. ≥ 3	2 (16%)	5 (83%)	0.005
Hospitalization for AEs	1 (8%)	4 (66%)	0.008
PD during treatment	1 (8%)	2 (40%)	0.13
PR + CR (as BMR)	8 (66%)	3 (60%)	0.7
PR + CR (last FU)	4 (33%)	2 (40%)	0.79

PhysA, physical activity; KI, kinase inhibitor; AEs, adverse events; Gr., grade; PD, progressive disease; PR, partial response; CR, complete response; BMR, best morphological response; and FU, follow-up.
Adverse event grade was assessed according to CTCAE, version 5.0; tumour response was assessed according to RECIST criteria, version 1.1.

(data not shown). Patients who were inactive at T0 had significantly higher rates of treatment interruptions compared to those who were mildly or highly active. This was significant during the first half of the FU period (85 vs 30% at T1, P = 0.01) and trended towards significance over the entire treatment course (85 vs 47% at T2, P = 0.08) (Table 1). No differences were found between patients needing KI interruption, in terms of sex (8/12 F vs 8/16 M, P = 0.38) and age (64.9 vs 57.7 years, P = 0.27) (data not shown). Although not statistically significant, other safety parameters also trended towards worse outcomes in the baseline inactive group. In particular, these patients experienced a higher incidence of >4 adverse events (AEs) (100% vs 60%, P = 0.15), more frequent grade ≥3 AEs (100% vs 40%, P = 0.37) and a higher frequency of progressive disease (PD) (42 vs 10% at T1, P = 0.05, and 42 vs 14% at T2, P = 0.15).

PFS, as assessed by Kaplan–Meier analysis, was shorter in patients who were inactive at baseline compared to mildly and highly active patients either considered separately or combined (46.1 vs 55.3 and 56.4 months, P = 0.351, and 46.1 vs 55.6 months, P = 0.151) (Fig. 2A).

Impact of physical activity decline on treatment tolerability and disease progression

Patients who experienced a decline in PhysA status during the FU demonstrated significantly poorer treatment tolerance and outcomes than those who maintained their baseline levels. In particular, the PhysA-declined group exhibited an increased frequency of treatment interruptions (100 vs 31%, P = 0.006), a higher incidence of >5 AEs (100 vs 31%, P = 0.006), a higher occurrence of grade ≥ 3 AEs (P = 0.01 for one event; P = 0.005 for two events) and higher hospitalization rates due to toxicities (66 vs 8%, P = 0.008) (Table 2). The Kaplan–Meier analysis confirmed a trend towards a shorter PFS in patients who experienced a decline in PhysA compared to those who maintained it (46.8 vs 59 months, P = 0.09) (Fig. 2B). A significant inverse correlation was observed between the decline in METs from baseline to the final FU and the number of AEs experienced (Pearson's r = −0.15, P = 0.04) (Fig. 3).

Five AEs were identified as the more-limiting patients' ability to engage in PhysA, based on their frequency and perceived intensity across the treatment period (T0–T2): fatigue, reported in 80% of patients; depression, in 80% of cases; diarrhoea, in 65% of patients; articular pain, in 60%; and cutaneous disorders in 53% of cases (Fig. 4).

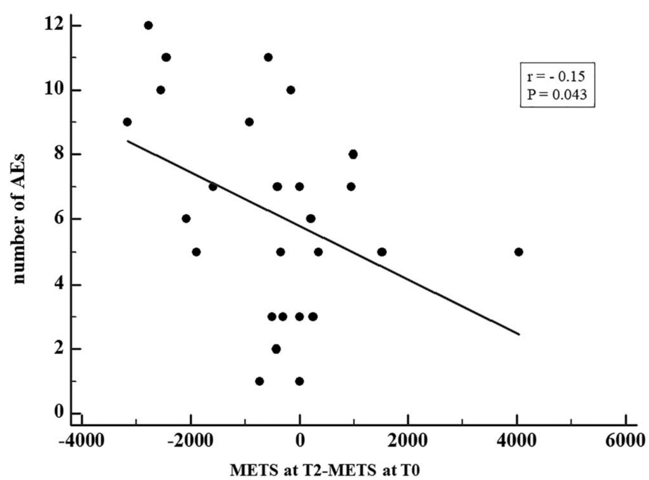

Figure 3

Linear regression analysis between metabolic equivalent (MET) loss and the number of adverse events (AEs). By performing a linear regression analysis between MET difference (final assessment T2 − basal assessment T0, thus representing the entity of MET loss) and the number of developed AEs during the follow-up (FU), a significant negative correlation is deduced (r 0.15, P 0.043).

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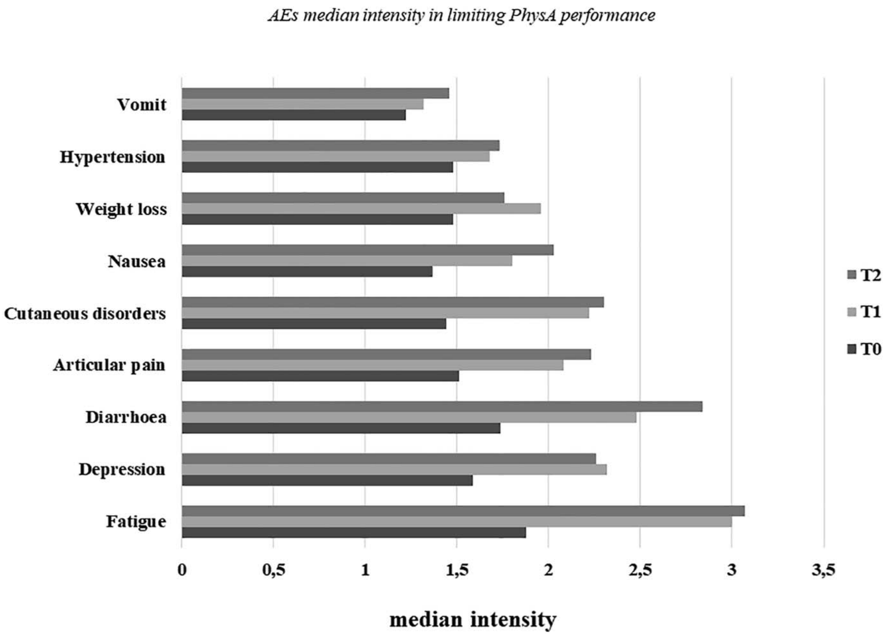

Figure 4

Adverse event median intensity in limiting physical activity (PhysA) performance. Patients were asked, for each time point (basal T0, intermediate T1 and final T2), which AEs and with which intensity (from 0 to 4) limited them in performing PhysA. Fatigue, depression, diarrhoea, articular pain and cutaneous disorders were the AEs mostly limiting their willingness or possibility to perform PhysA.

Discussion

We report, for the first time, the role of PhysA levels and their maintenance over time in a cohort of patients with advanced thyroid cancer on KI therapy. Our findings suggest that both baseline PhysA status and its longitudinal maintenance are significantly associated and/or trend towards significance with treatment safety and efficacy profiles, including the incidence/grade of AEs, treatment interruptions and PFS. Approximately 25% of patients were classified as physically inactive at baseline, and these individuals experienced worse outcomes across multiple domains. In particular, inactive patients trended towards significantly higher rates of treatment interruptions, more grade ≥ 3 AEs, and had more frequently a progressive disease. Although some of these differences did not reach statistical significance, the observed trends suggest a clinically relevant association between inactivity and suboptimal treatment outcomes.

Importantly, the maintenance of PhysA during treatment emerged as a stronger predictor of favourable outcomes than baseline PhysA. Indeed, patients who preserved their fitness throughout the FU had lower rates of treatment interruptions, fewer severe AEs and a longer PFS compared to those who experienced a decline in activity levels. Moreover, a significant inverse correlation was observed between the decline in METs and the number of AEs experienced, reinforcing the protective role of sustained PhysA in mitigating treatment toxicity.

Our results are consistent with the emerging literature in other oncologic settings. In hepatocellular carcinoma, Liu *et al.* demonstrated that patients who remained physically active during treatment with lenvatinib and/or immune checkpoint inhibitors had a better overall and progression-free survival and an improved tolerance to treatment-related toxicities (26). Similarly, multimodal prehabilitation programmes, incorporating structured exercise, have shown benefits in surgical and medical oncology settings by enhancing physical resilience, reducing complications and improving functional outcomes (18, 19, 20, 26, 27). No data specifically addressing the impact of PhysA in TC patients on KI therapy are available, but our findings suggest that similar principles may apply. Both antiangiogenetic and target drugs are known to induce a range of debilitating toxicities, including fatigue, anorexia, sarcopenia and mood distress, which can lead to a reduced physical function and further exacerbate treatment intolerance (15, 16, 17). In our cohort, fatigue, depression and gastrointestinal side effects were the most frequently reported barriers to physical activity. These findings underscore the bidirectional relationship between treatment-related toxicities and a reduced physical activity, suggesting a potential feedback loop negatively impacting both patient QoL and treatment outcomes.

This study has some limitations. In particular, the retrospective design, based on post hoc questionnaires based on patients' memories, limits the ability to infer causality. AEs such as fatigue, depression and diarrhoea, whose intensity increases during treatment, are likely responsible for the reduction in PhysA observed in some patients. Nevertheless, patients able to keep or even increase their activity despite the toxicities experienced a better tolerance and PFS. PhysA was assessed using self-reported questionnaires, which may be subjected to recall or reporting bias.

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Although we adopted a validated and widely used instrument (IPAQ), other objective measures could enhance data reliability in future prospective studies. It should also be highlighted that the heterogeneity of the cohort in terms of tumour subtype and treatment duration could have introduced confounding factors not fully accounted for in the analysis. Moreover, we analysed patients treated with MKIs and target therapies, which are known to have a better safety profile in terms of AEs. However, a sub-analysis was not statistically feasible for the small numbers of the cohort. Finally, we did not prescribe to patients a specific physical activity to be introduced or implemented during treatment, but, in line with the data available for other cancers, it could be hypothesized that a well-structured and tailored training programme could have led to even more significant results.

These exploratory findings, however, support the rationale for prospective interventional trials with objective activity monitoring, structured and supervised exercise prescriptions, larger and more homogeneous cohorts and pre-specified outcomes.

Conclusion

This is the first study showing that maintaining adequate physical activity levels is associated with better treatment tolerance and outcomes in advanced thyroid cancer patients on kinase inhibitor therapy, supporting the need for prospective prehabilitation trials. The modified IPAQs used in this study are easy to apply, making them a feasible tool for routine PhysA assessment in clinical practice. Early identification of patients at risk of physical decline, combined with targeted exercises and supportive care strategies, may enhance treatment compliance and disease outcomes.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/JOE-24-0078.

Declaration of interest

LF is a consultant for Eisai, Ipsen and Lilly. The remaining authors have nothing to disclose.

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Author contribution statement

CC and DC conceived the study, collected the data, performed formal analysis and wrote and edited the manuscript; FC, MS, SDL, MT, CM and ML collected the data, performed formal analysis and edited the manuscript; LF and LP supervised the study; and CC, DC and LF conceived and supervised the study and wrote the manuscript. All authors were responsible for the final approval of the manuscript.

References

1 Durante C, Haddy N, Baudin E, *et al.* Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *J Clin Endocrinol Metab* 2006 **91** 2892–2899. (https://doi.org/10.1210/jc.2005-2838)

2 Schlumberger M, Bastholt L, Dralle H, *et al.* 2012 European thyroid association guidelines for metastatic medullary thyroid cancer. *Eur Thyroid J* 2012 **1** 5–14. (https://doi.org/10.1159/000336977)

3 Fugazzola L, Elisei R, Fuhrer D, *et al.* 2019 European Thyroid Association guidelines for the treatment and follow-up of advanced radioiodine-refractory thyroid cancer. *Eur Thyroid J* 2019 **8** 227–245. (https://doi.org/10.1159/000502229)

4 European Medicines Agency. *EMEA/H/C/00592 – Human Medicine European Public Assessment Report (EPAR): Sorafenib Accord 2022*. Amsterdam, The Netherlands: EMA, 2022. (https://www.ema.europa.eu/en/medicines/human/EPAR/nexavar)

5 European Medicines Agency. *EMEA/H/C/003727 – IG/1641 – Human Medicine European Public Assessment Report (EPAR): Lenima 2023*. Amsterdam, The Netherlands: EMA, 2023. (https://www.ema.europa.eu/en/medicines/human/EPAR/lenvima)

6 European Medicines Agency. *EMEA/H/C/002640 – II/0053 – Human Medicine European Public Assessment Report (EPAR): Cometriq 2023*. Amsterdam, The Netherlands: EMA, 2023. (https://www.ema.europa.eu/en/medicines/human/EPAR/cometriq)

7 European Medicines Agency. *EMEA/H/C/002315 – IAIN/0060G – Human Medicine European Public Assessment Report (EPAR): Caprelsa 2023*. Amsterdam, The Netherlands: EMA, 2023. (https://www.ema.europa.eu/en/medicines/human/EPAR/caprelsa)

8 European Medicines Agency. *EMEA/H/C/005375 – PSUSA/00010917/202211 – Human Medicine European Public Assessment Report (EPAR): Retsevmo 2023*. Amsterdam, The Netherlands: EMA, 2023. (https://www.ema.europa.eu/en/medicines/human/EPAR/retsevmo)

9 European Medicines Agency. *EMEA/H/C/004919 – II/0030 – Human Medicine European Public Assessment Report (EPAR): Vitrakvi 2023*. Amsterdam, The Netherlands: EMA, 2023. (https://www.ema.europa.eu/en/medicines/human/EPAR/vitrakvi)

10 Brose MS, Nutting CM, Jarzab B, *et al.* Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet* 2014 **384** 319–328. (https://doi.org/10.1016/s0140-6736(14)60421-9)

11 Schlumberger M, Tahara M, Wirth LJ, *et al.* Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med* 2015 **372** 621–630. (https://doi.org/10.1056/nejmoa1406470)

12 Wells SA Jr, Robinson BG, Gagel RF, *et al.* Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol* 2012 **30** 134–141. (https://doi.org/10.1200/jco.2011.35.5040)

13 Elisei R, Schlumberger MJ, Müller SP, *et al*. Cabozantinib in progressive medullary thyroid cancer. *J Clin Oncol* 2013 **29** 3639–3646. (https://doi.org/10.1200/JCO.2012.48.4659)

14 Wirth LJ, Sherman E, Robinson B, *et al.* Efficacy of selpercatinib in RET-altered thyroid cancers. *N Engl J Med* 2020 **383** 825–835. (https://doi.org/10.1056/nejmoa2005651)

15 Shyam Sunder S, Sharma UC & Pokharel S. Adverse effects of tyrosine kinase inhibitors in cancer therapy: pathophysiology, mechanisms and clinical management. *Signal Transduction Target Ther* 2023 **8** 262. (https://doi.org/10.1038/s41392-023-01469-6)

16 De Leo S, Colombo C, Di Stefano M, *et al*. Body composition and leptin/ghrelin levels during lenvatinib for thyroid cancer. *Eur Thyroid J* 2020 **1** 1–10. (https://doi.org/10.1159/000504048)

17 Dalmiglio C, Brilli L, Ciuoli C, *et al.* Effect of pre-existent sarcopenia on oncological outcome of advanced thyroid cancer patients treated with tyrosine kinase inhibitors. *Cancers* 2022 **19** 4569. (https://doi.org/10.3390/cancers14194569)

18 Amirkhosravi F, Allenson KC, Moore LW, *et al.* Multimodal prehabilitation and postoperative outcomes in upper abdominal surgery: systematic review and meta-analysis. *Sci Rep* 2024 **14** 16012. (https://doi.org/10.1038/s41598-024-66633-6)

19 Kirkham AA, Shave RE, Bland KA, *et al.* Protective effects of acute exercise prior to doxorubicin on cardiac function of breast cancer patients: a proof-of-concept RCT. *Int J Cardiol* 2017 **245** 263–270. (https://doi.org/10.1016/j.ijcard.2017.07.037)

20 Jack S, Andritsch E, Joaquim A, *et al.* Current landscape and support for practical initiation of oncological prehabilitation translatable to thyroid cancer: a position paper. *Heliyon* 2024 **10** e30723. (https://doi.org/10.1016/j.heliyon.2024.e30723)

21 World Medical Association. World medical association declaration of Helsinki: ethical principles for medical research involving human participants. *J Am Med Assoc* 2025 **333** 71–74. (https://doi.org/10.1001/jama.2024.21972)

22 Eisenhauer EA, Therasse P, Bogaerts J, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009 **45** 228–247. (https://doi.org/10.1016/j.ejca.2008.10.026)

23 Ainsworth BE, Haskell WL, Whitt MC, *et al.* Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000 **32** 498–504. (https://doi.org/10.1097/00005768-200009001-00009)

24 Cleland C, Ferguson S, Ellis G, *et al.* Validity of the International Physical Activity Questionnaire (IPAQ) for assessing moderate-to-vigorous physical activity and sedentary behaviour of older adults in the United Kingdom. *BMC Med Res Methodol* 2018 **1** 176. (https://doi.org/10.1186/s12874-018-0642-3)

25 Scherr J, Wolfarth B, Christle JW, *et al.* Associations between Borg's rating of perceived exertion and physiological measures of exercise intensity. *Eur J Appl Physiol* 2013 **113** 147–155. (https://doi.org/10.1007/s00421-012-2421-x)

26 Liu XF, Zhu XD, Feng LH, *et al.* Physical activity improves outcomes of combined lenvatinib plus anti-PD-1 therapy in unresectable hepatocellular carcinoma: a retrospective study and mouse model. *Exp Hematol Oncol* 2022 **11** 20. (https://doi.org/10.1186/s40164-022-00275-0)

27 Coderre D, Brahmbhatt P, Hunter TL, *et al.* Cancer prehabilitation in practice: the current evidence. *Curr Oncol Rep* 2022 **24** 1569–1577. (https://doi.org/10.1007/s11912-022-01304-1)