Adverse Events Reporting of Clinical Trials in Exercise Oncology Research (ADVANCE): Protocol for a Scoping Review

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Introduction: Adequate, transparent, and consistent reporting of adverse events (AEs) in exercise oncology trials is critical to assess the safety of exercise interventions for people following a cancer diagnosis. However, there is little understanding of how AEs are reported in exercise oncology trials. Thus, we propose to conduct a scoping review to summarise and evaluate current practice of reporting of AEs in published exercise oncology trials with further exploration of factors associated with inadequate reporting of AEs. The study findings will serve to inform the need for future research on standardisation of the definition, collection, and reporting of AEs for exercise oncology research.

Materials and Methods: The ADVANCE (ADverse eVents reporting of clinicAl trials iN exerciSe oncology rEsearch) study will be conducted and reported following the PRISMA extension for scoping reviews guideline. Any type of clinical trial involving an exercise intervention in people living with and beyond cancer with a full-text report in English will be included. Six electronic databases (Embase, PubMed, Google Scholar, Web of Science Core Collection, SPORTDiscus, and CINAHL Plus) will be searched for studies. Two independent review authors will assess eligibility of identified studies, chart data using pre-established extraction forms, and evaluate adequacy of reporting of AEs-related data against a 20-item scoring checklist derived from the CONSORT (Consolidated Standards of Reporting Trials) harms extension. We will summarise results using descriptive and inferential analysis methods.

Ethics and Dissemination: No ethics approval will be required to conduct the ADVANCE study owing to inclusion of only published data. The study results will be disseminated via publications in peer-reviewed journals and presentations at national and international conferences.

Systematic Review Registration: Open Science Framework: https://osf.io/NXEJD/ (doi:10.17605/OSF.IO/NXEJD).

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INTRODUCTION

Exercise is emerging as a therapy in supportive oncology care for people living with and beyond cancer (1). There is substantial evidence that exercise can provide an abundance of benefits, including improving physical structure and function, cancer-related fatigue, psychological distress and quality of life (2–5), increasing resilience prior to surgery and rehabilitation after surgery, as well as reducing disease specific and overall mortality risk (6, 7). In this context, accurate knowledge of safety profiles of exercise interventions is crucial for health policy makers and healthcare providers to critically appraise the utility of an exercise intervention and can facilitate informed decision making for cancer patients and survivors considering exercise therapy. Lack of confidence in findings of harms from clinical exercise trials can hinder implementation of exercise therapy as part of standard oncology care (1, 8, 9). This is particularly true for people with an aggressive malignancy (e.g., pancreatic ductal adenocarcinoma), advanced disease, and/or older age as well as patients during active oncological treatments, where safety concerns of exercise may be more prominent (9–11). Thus, complete and clear reporting of adverse events (AEs) in exercise oncology trials is warranted for the purpose of identifying and quantifying potential harms of exercise interventions.

Exercise has been repeatedly reported as a safe intervention strategy in people following a cancer diagnosis regardless of age, disease type and stage, and oncological treatment (11–15). However, these findings may be related to the absence of or inadequate analysis and presentation of AEs data in reports of exercise oncology studies. For example, systematic reviews and meta-analyses examining safety of exercise interventions in adult cancer patients and survivors indicated that up to 60% of the included studies made no mention of AEs (i.e., whether or not there was an AE) (11, 13–16). In addition, data for health-related withdrawals and discontinuations is an important source of information on potential harms of healthcare interventions (17, 18). Nevertheless, exercise researchers often neglect to report and categorise such data as AEs in their trial reports (including studies in cancer patients and survivors) (11, 19), suggesting understatement and incomplete reporting of AEs. Of importance, methods for definition, collection and reporting of AEs have not yet been standardised for exercise oncology trials, which can limit current safety findings in this field (1, 20).

Although AEs reported in exercise trials for people following a cancer diagnosis (mostly breast) have been extensively examined (11–16), there is little understanding of the methods used for defining, collecting, presenting and analysing AEs and the patterns of reporting of AEs data in exercise oncology trials. Additionally, the completeness of reporting of AEs-related data have not yet been evaluated objectively. Therefore, we propose to undertake a scoping review to identify and map published trials of exercise interventions in people following a cancer diagnosis reporting AEs, and summarise their characteristics of reporting of AEs-related data. Further, we will quantify completeness of AEs reporting, and explore factors associated with suboptimal reporting of AEs. Results of the ADVANCE (ADVerse eVents reporting of clinicAI trials in exerCise oncology rEsearch) study will serve to inform the need for the development of consensus guidelines specific to clinical exercise trials in oncology for the definition, collection, and reporting of AEs.

MATERIALS AND METHODS

The study protocol was developed following the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (21), and reported according to the PRISMA-Protocols 2015 checklist (S1 Appendix) (22, 23). The study is registered with Open Science Framework (OSF): https://osf.io/NXEJD/ (doi:10.17605/OSF.IO/NXEJD).

Eligibility Criteria

We will use the following study characteristics and report characteristics as criteria to select studies for the ADVANCE study (Table 1).

Study Characteristics

Study Designs

We will include any type of interventional study design, including randomised controlled trials (RCTs), non-RCTs, single-arm trials/ case series (24), and case reports. Observational study designs where interventions were not assigned to participants by a study investigator (25) will be excluded.

Participants

We will include studies in people following a cancer diagnosis, regardless of their age, sex, cancer site, disease stage, and treatment status (before, during or after any oncological treatment, such as chemotherapy, radiotherapy, and surgery). Studies in mixed cohorts of participants with or without an active/past oncological condition will be excluded unless AEs data were reported separately for involved cancer patients and survivors.

Interventions

Interventions of interest are any form of structured (planned, individualised, and repetitive) exercise training that involves large skeletal muscle groups and incorporates training stimuli in aerobic fitness, muscle strength/endurance/power, flexibility, balance, and/or coordination (26). These will include: (i) traditional resistance, aerobic, and sensorimotor exercises, (ii) mind-body exercises (e.g., Qigong, Tai Chi, Yoga, and Pilates), (iii) sports (activities that require physical effort and skills with predetermined rules and objectives) and adapted sport activities (27), and (iv) video-game based exercises. Multimodal interventions where exercise was complemented by non-exercise components (e.g., dietary/nutritional support and psychological counselling) will be included. Moreover, interventions in which exercise was performed along with an additional training modality (e.g., whole-body vibration and neuromuscular electrical stimulation) will be included. There will be no restrictions on exercise settings (e.g., clinics, gymnasiums/community areas, and homes) and surroundings (i.e., on land or in water), supervision, delivery mode (e.g., one-on-one, paired, and in a small group), equipment, and prescriptions in terms of duration, frequency, volume, intensity, and progression.
TABLE 1 | An overview of eligibility criteria.

| Categories | Inclusion criteria | Exclusion criteria |
|------------|--------------------|-------------------|
| **Study characteristics** | | |
| Study designs | Any type of interventional study design, including RCTs, non-RCTs, single-arm trials/case series, and case reports | Observational studies |
| Participants* | People living with and beyond cancer | Mixed cohorts of participants with or without an active/past oncological condition |
| Interventions† | Any form of planned, individualised and repetitive exercise training (including structured walking exercise) | Non-recreational physical activity interventions [i.e., occupation, transportation, and housework] |
| Comparators | No restrictions | Specific musculoskeletal rehabilitation interventions (e.g., pelvic floor muscle exercises) |
| Outcomes | No restrictions on outcomes of interest or whether reporting AEs occurred | Interventions used solely static muscle stretching |
| Length of follow-up | No restrictions | |
| **Report characteristics** | | |
| Language | Only English | |
| Publication status | Only full text publications in peer-reviewed journals | |
| Year of publication | No restrictions | |

*Studies in mixed cohorts of participants will be included when adverse events data were reported separately for cancer patients and survivors.
†Studies using multimodal interventions in which exercise was complemented by non-exercise components (e.g., dietary/nutritional support) or performed with an additional training modality (e.g., whole-body vibration) will be included.
AE, adverse event; RCTs, randomised controlled trials.

Any non-structured physical activity intervention and interventions that used non-leisure-time physical activities (i.e., occupation, transportation, and housework) will be excluded. We will also exclude interventions that focused on specific musculoskeletal rehabilitation (e.g., pelvic floor muscle exercises and swallowing exercises) and/or used exclusively static muscle stretching. Walking will be considered as an aerobic-based exercise when it was individually tailored and used appropriately.

Comparators
Given that different types of interventional study designs will be included, we will not select studies based on whether there is a comparator or what comparative interventions were used.

Outcomes
To provide a comprehensive overview regarding current practice of AEs reporting, we will not select studies based on reported outcome measures. With regard to AEs, we will consider any harmful outcome that occurred over the course of the trial (including the follow-up period after the prescribed exercise intervention) and was explicitly reported in the included trial reports, irrespective of the relatedness to the exercise intervention undertaken. This is to take account of potential variations in the definition of an AE in current exercise oncology research and the fact that determination of relatedness of AEs to the prescribed intervention is largely subjective and with unknown validity (17, 28). In addition, occurrence of health-related withdrawals and discontinuations will be considered as AEs. Similarly, occurrence of non-attendance, nonadherence and intolerability to exercise interventions/testing due to health reasons will also be considered as AEs.

Length of Follow-Up
There will be no restrictions on the length of follow-up post exercise intervention.

Report Characteristics
We will only include full-text reports that were written in English and published in peer-reviewed journals. There will be no restrictions placed on year of publication.

Information Sources
To ensure transparency and maximize reproducibility of literature searches, we will follow the PRISMA extension for literature search in reporting search components for this review (29). We will search six databases from the date of inception, including PubMed, Embase (Embase.com), Web of Science Core Collection (webofknowledge.com), Google Scholar, SPORTDiscus (EBSCOhost), and CINAHL Plus (EBSCOhost). As the ADVANCE study will focus exclusively on published exercise oncology trials and the reporting practice for AEs-related data, we will not adopt any additional information source (e.g., grey literature and contacting authors of included trials).

Search Strategy
Literature search strategies will be developed by the review team, which will be reviewed by a subject librarian at Edith Cowan University (ECU) and refined accordingly. Detailed search strategies of all selected databases will be provided in the final reports of the study. A draft search strategy for PubMed is provided in S2 Appendix. Only thesaurus and free-text terms related to ‘cancer’ and ‘exercise’ will be used in electronic searches. Given the databases selected and relatively broad search terms to be used, the planned electronic searching will provide sufficient evidence for the study. As a result, we will not employ any additional search method to identify studies (e.g., citation searching).

Study Selection
Records yielded from database searching will be exported and stored in Covidence (Veritas Health Innovation Ltd, Melbourne VIC, Australia). Only the maximum number of results that can be
displayed in Google Scholar for a particular search query (up to n = 1000) will be screened (29). Duplicates will be removed either automatically (using Covidence) or manually. After de-duplication, two independent reviewers will select studies against the eligibility criteria. At the title and abstract screening stage, records will only be excluded if explicitly identified as: (i) editorials, commentaries, and letters, (ii) non-experimental (including reviews/meta-analyses, study protocols, observational studies (25), and qualitative studies) and preclinical observational studies, or (iii) delivering no exercise interventions or exercise as a subordinate intervention. This is to prevent exclusion of records where AEs were not addressed in titles and abstracts of included trial reports. For studies with duplicate publications reporting AEs, if the number of participants reported was different across publications, the article involving the highest number of participants will be considered as the main report and thus included; when the number of participants was reported consistently across different trial reports, we will refer to the first article resulting from the trial. In addition, we will refer to the first article when none of the resultant publications of a trial reported AEs. However, if trials with duplicate publications only addressed AEs in one of the reports, this report will be included regardless of the number of participants involved or date of publication. Any disagreement will be addressed through discussion between the two review authors or (if needed) adjudication by a third reviewer.

**Data Extraction and Evaluation of Completeness of AEs Reporting**

Two independent reviewers will chart data from included trial reports using pre-established, structured extraction forms that will be piloted and refined accordingly to ensure all relevant data can be captured. Any discrepancy will be resolved through discussion between the two reviewers or (if needed) adjudication by a third reviewer. Draft data extraction forms are provided in Tables 2, 3. In addition, elaboration and explanation documents for the forms will be provided to minimise inconsistencies in data extraction (S3, S4 Appendices).

We will extract trial parameters that may affect reporting of AEs for all included trials (Table 2 and S3 Appendix) (30–32), including: (i) general publication information (year of publication, journal impact factor, and trial funding), (ii) study characteristics (trial location, study design, nature of controls (if applicable), trial phase (if applicable), study setting (i.e., single- or multi-centre), and whether or not study of AEs was a primary outcome), (iii) participant characteristics (sample size, age, cancer site, disease stage, and cancer treatment status), and (iv) characteristics of the exercise intervention (mode, length of intervention, frequency, session duration, intensity, and supervision).

Whether there was reporting of AEs in the included studies will be recorded as ‘Yes’, ‘No’, or ‘Yes, but only as generic statements’ (e.g., ‘no serious AEs occurred’ or ‘the exercise program was generally safe and well tolerated’). For studies identified as ‘Yes’ (including studies that reported AEs in generic statements), we will further extract data pertinent to AEs using a 20-item checklist derived from the 10 recommendations in the CONSORT (Consolidated Standards of Reporting Trials) extension for reporting of harms-related data (17) (Table 3 and S4 Appendix). These items will address various aspects of AEs reporting in different sections of a paper from the title/abstract to the discussion section. Specifically, information will be captured regarding (i) whether or not mentioning of AEs in the title/abstract (item 1) and the introduction section (item 2), (ii) approaches to definition, collection, presentation and analysis of AEs (items 3a-5), (iii) appropriateness in describing AEs results (including health-related withdrawals and discontinuations, and tolerability of exercise training/testing) (items 6a-9), and (iv) whether or not there was a discussion of AEs findings (items 10a-10c). When pertinent, each item will be rated as ‘yes’ or ‘no’ depending on whether or not the information was reported properly in the specified section. Similar to previous studies that used the CONSORT harms criteria appraising quality of reporting of AEs in clinical trials (31, 33, 34), a score of 1 or 0 will be given to items rated as ‘yes’ or ‘no’ with equal weight attributed to each item. As such, the completeness of reporting of AEs-related data for a trial report will be determined by a sum score calculated based on the applicable items in the checklist with higher scores indicating greater data adequacy.

Additionally, we will quantify the relative emphasis given to reporting of AEs in included RCTs using the method recommended by Ioannidis et al. (30, 35). This approach has been widely used by others as an objective measure complementary to quality assessment of reporting of AEs in RCTs (36–38). Specifically, we will calculate the extent of printed space dedicated to reporting of AEs in the results section and the proportion it represents of the entire results section. The printed space occupied by AEs data in the results section will be calculated as S/(N×Y) pages, where S is the length in centimeters of the results section for reporting of AEs, N is the number of columns on a printed page, and Y is the length in centimeters of the print area on a page (excluding upper and lower margins). Where available, subheadings concerning AEs [e.g., “Safety, tolerance, and attendance of the exercise program” (39)] will be included in the space calculation. All measurements will be performed using the Measuring Tool in Adobe Acrobat Reader DC (Adobe Inc., San Jose, CA) and reported with a 0.05-page resolution. Further, the number of tables and figures devoted to or containing AEs data in included RCTs will be recorded (including any presented in Supplementary Materials); however, the space occupied by tables and figures will not be included in the calculations described above.

**Critical Appraisal of Included Studies**

We will not appraise methodological quality or risk of bias of included studies to provide a comprehensive overview of AEs reporting in current exercise oncology trials. This is consistent with the PRISMA-ScR statement considering critical appraisal of individual sources of evidence as an optional step (21).

**Data Analysis**

We will use Cohen’s kappa coefficient (40) with 95% confidence intervals to assess inter-rater reliability of study selection and data extraction. The total number of studies that reported AEs will be counted and the proportion of studies...
reporting AEs will be summarised as per study design (i.e., RCTs, non-RCTs, single-group trials/case series, and case reports). In addition, the number of items met in the checklist (Table 3) for studies of a specific category (as per trial characteristics), and the extent of printed space dedicated to AEs reporting in the results section and the proportion it represents of the entire results section in RCTs will be analysed descriptively.

Independent samples t-test or one-way analysis of variance will be performed to compare the mean number of items met in the checklist (i.e., mean sum score) between groups of studies of a specific study design (e.g., funded RCTs vs. unfunded RCTs). In a similar fashion, the extent of printed space for AEs reporting in the results section and the proportion it represents of the entire results section in RCTs with different trial characteristics will be compared. Given that the checklist items in title/abstract,
### Title and abstract

1. If the study collected data on harms and benefits, the title or abstract should so state.

   

### Introduction

2. If the trial addresses both harms and benefits, the introduction should so state.

### Methods

3. List addressed adverse events with definitions for each (with attention, when relevant, to grading, expected vs. unexpected events, reference to standardized and validated definitions, and description of new definitions).

4. Clarify how harms-related information was collected (mode of data collection, timing, attribution methods, intensity of ascertainment, and harms-related monitoring and stopping rules, if pertinent).

5. Describe plans for presenting and analysing information on harms (including coding, handling of recurrent events, specification of timing issues, handling of continuous measures, and any statistical analyses).

### Results

6. Describe for each arm the participant withdrawals that are due to harms and the experience with the allocated treatment.

7. Provide the denominators for analyses on harms.

8. Present the absolute risk of each adverse event (specifying type, grade, and seriousness per arm), and present appropriate metrics for recurrent events, continuous variables and scale variables, whenever pertinent.

### Checklist for reporting of adverse events-related data

- **1.** If the study of harms was a primary outcome, did the title mention the word ‘harms’ or related terms/phrases or a specific event of interest, or was the information on harms presented in the abstract (including generic statements, e.g., “no adverse events occurred”)?
  
  - **2.** If the trial intended to investigate both harms and benefits, was there a balanced presentation of possible benefits and harms of exercise for cancer patients and survivors in the Introduction section?
  
  - **3a.** Did the author(s) define the types of adverse events intending to monitor or the recorded adverse events for the study?
  
  - **3b.** Did the author(s) clarify if the reported adverse events included all the adverse events collected or a selected sample?
  
  - **3c.** Were the author(s) explicit about separately reporting expected and unexpected adverse events?
  
  - **4a.** Was the mode of adverse events collection specified (i.e., active vs. passive surveillance of harms)?
  
  - **4b.** Was the time frame of monitoring for adverse events reported?
  
  - **4c.** If relatedness of collected adverse events to the exercise intervention/testing or cancer treatments undertaken was assigned, did the author(s) specify the attribution process?
  
  - **4d.** Did the author(s) specify rules to discontinue allocated exercise intervention for harms-related reasons?
  
  - **5.** Did the author(s) report plans for presenting and analysing adverse events data?
  
  - **6a.** Did the author(s) report the number of participants who withdrew due to adverse events (including death) appropriately?
  
  - **6b.** Did the author(s) report the number of participants who discontinued or were not adherent to the allocated exercise intervention due to adverse events appropriately?
  
  - **6c.** If there was reporting of withdrawals or discontinuations due to adverse events, did the author(s) report their timing of occurrence appropriately?
  
  - **7.** If there were analyses of adverse events data, did the author(s) specify the denominators (i.e., the total number of participants and total follow-up time included in each analysis)?
  
  - **8a.** If there were adverse events, did the author(s) report the incidence or frequency for each type and severity category (if relevant) of adverse event appropriately? Alternatively, if there were no adverse events of a specific type and severity, did the author(s) so state?
introduction and discussion sections are optional, we will perform subgroup analyses of the completeness of AEs reporting (as per mean sum score) for RCTs and non-RCTs that were intended for both harms and efficacy outcomes or for efficacy outcomes alone.

Logistic regression will be performed to examine whether there are any predictors of reporting of an individual item in the checklist. This will be undertaken as per types of study design. The predictors that will be considered in the analysis include: year of publication, journal impact factor, trial funding, trial location, type of control, participants characteristics (including sample size, age, cancer site and stage, and cancer treatment status), exercise interventions characteristics (including mode, length, frequency, session duration, intensity, and supervision), and whether or not study of AEs was a primary outcome.

Statistical analyses will be performed using the latest version of R available at the time of analysis (https://www.r-project.org/). All tests will be two-tailed and a $p$-value $\leq 0.05$ will be considered statistically significant.

**Ethics and Dissemination**

No ethics approval will be required to conduct the ADVANCE study owing to inclusion of only published data. If there are any modifications to the study protocol, they will be reflected in the OSF registry (https://osf.io/NXEJD/) and in the final reports for the ADVANCE study. We will disseminate the study results via publications in peer-reviewed journals and presentations at national and international conferences. Additionally, findings of the ADVANCE study will be discussed with relevant stakeholders (including healthcare professionals, health policy makers, exercise oncology researchers, and cancer patients and survivors) to determine whether there is a need for the development of guidelines for reporting of AEs specific to exercise oncology trials.

**DISCUSSION**

Adequate, transparent, and consistent reporting of AEs in exercise oncology trials is crucial to assess the safety of exercise interventions in people living with and beyond cancer. However, there is little knowledge with respect to how AEs are reported in exercise oncology trials. To this end, the ADVANCE study is proposed to review current practice of reporting of AEs in the field of exercise oncology.

There are several strengths for the ADVANCE study. First, the study will include any type of interventional study design so as to provide a comprehensive overview of reporting of AEs in exercise oncology trials. Second, a pre-defined scoring system and an empirically-tested measure will be adopted to quantify the completeness of AEs reporting in all included trials or the

| TABLE 3 | Continued |
| --- | --- |
| Title of trial report: | Name of lead author: |
| **Paper section** | **Item no.** | **CONSORT harms recommendations** | **Checklist for reporting of adverse events-related data** | **Rating (Y=1, N=0)** | **If yes, provide page no.** |
| Discussion | 9 | Describe any subgroup analyses and exploratory analyses for harms. | 9*8b. Did the author(s) report the number of affected participants for each type and severity category (if relevant) of adverse event appropriately? | ☐ ☐ ☐ |
| | 10 | Provide a balanced discussion of benefits and harms with emphasis on study limitations, generalizability, and other sources of information on harms. | 10a. If the author(s) intended to investigate both harms and benefits or reported occurrence of adverse events, was there a balanced discussion on efficacy and harms (including no adverse events occurred) findings of the exercise intervention? | ☐ ☐ ☐ |
| | | | 11b. If there was intention to investigate harms of an exercise intervention, did the author(s) discuss study limitations specific to adverse events findings (e.g., inconclusive findings, lack of power, lack of generalisability, etc)? | ☐ ☐ ☐ |
| | | | 10c. If the author(s) intended to investigate both harms and benefits or reported occurrence of adverse events, was there a discussion of any previous evidence on harms findings of exercise in cancer patients and survivors (including data derived from a pilot study of the exercise intervention)? | ☐ ☐ ☐ |

Modified from: Ioannidis JP, Evans SJ, Gotzsche PC, O’Neill RT, Altman DG, Schulz K, Moher D, CONSORT Group. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med. 2004;141:781-788.

*Item not required for case reports.
*Item not required for studies that did not have concurrent controls, including single-arm trials/case series and case reports.

*Y, no; Y, yes; NA, not applicable.*
relative importance attached to reporting of AEs results in the included reports for RCTs. Third, various analyses will be performed to identify any trial-related parameters associated with suboptimal reporting of AEs in order to formulate suggestions for how to improve AEs reporting in future exercise oncology trials. Lastly, studies will be identified through rigorous searches in multiple broad disciplinary (i.e., Embase, PubMed, Web of Science Core Collection, and Google Scholar) and subject-specific (i.e., SPORTDiscus and CINAHL Plus) databases. The combination of these databases has been shown to provide adequate and efficient results for reviews on the topics of allied health (41). A limitation of the ADVANCE study is that only full-text trial reports written in English and published in peer-reviewed journals will be included. However, the evidence base derived from published trials in English would be sufficient to provide a comprehensive picture of current practice of reporting of AEs in exercise oncology trials.

In conclusion, the ADVANCE study will be able to improve our understanding of how AEs are reported and provide directions for future research efforts to standardise reporting of AEs in exercise oncology trials.

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**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

**AUTHOR CONTRIBUTIONS**

HL and OS conceptualized and designed the study, and developed the first draft of the manuscript. DG, RN, and DT conceptualized and designed the study, and critically revised the manuscript. All authors read and approved the final version of the manuscript.

**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.841266/full#supplementary-material
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