REPORTING OF TOBACCO USE AND TOBACCO-RELATED ANALYSES IN CANCER COOPERATIVE GROUP CLINICAL TRIALS: A SYSTEMATIC SCOPING REVIEW

L. Eng1, J. Brual1, A. Nagee2, S. Mok2, R. Fazelzad3, M. Chaiton4, D. P. Saunders5, N. Mittmann6, R. Truscott7, G. Liu1, P. A. Bradbury9, W. K. Evans9, J. Papadakos9 & M. E. Giuliani10*

1Division of Medical Oncology and Hematology, Department of Medicine, Princess Margaret Cancer Centre/University Health Network and University of Toronto, Toronto; 2Cancer Education Program, Princess Margaret Cancer Centre, Toronto; 3Library and Information Services, Princess Margaret Cancer Centre, University Health Network, Toronto; 4Centre for Addiction and Mental Health, University of Toronto, Toronto; 5Northeast Cancer Centre of Health Sciences North, Northern Ontario School of Medicine, Sudbury; 6Canadian Agency for Drugs and Technologies in Health, Toronto; 7Division of Prevention Policy and Stakeholder Engagement, Ontario Health (Cancer Care Ontario), Toronto; 8Department of Oncology, McMaster University, Hamilton; 9Patient Education, Ontario Health (Cancer Care Ontario), Toronto; 10Department of Radiation Oncology, Princess Margaret Cancer Centre, Toronto, Canada

Available online 7 November 2022

Background: Continued smoking after a diagnosis of cancer negatively impacts cancer outcomes, but the impact of tobacco on newer treatments options is not well established. Collecting and evaluating tobacco use in clinical trials may advance understanding of the consequences of tobacco use on treatment modalities, but little is known about the frequency of reporting and analysis of tobacco use in cancer cooperative clinical trial groups.

Patients and methods: A comprehensive literature search was conducted to identify cancer cooperative group clinical trials published from January 2017-October 2019. Eligible studies evaluated either systemic and/or radiation therapies, included ≥100 adult patients, and reported on at least one of: overall survival, disease/progression-free survival, response rates, toxicities/adverse events, or quality-of-life.

Results: A total of 91 studies representing 90 trials met inclusion criteria with trial start dates ranging from 1995 to 2015 with 14% involving lung and 5% head and neck cancer patients. A total of 19 studies reported baseline tobacco use; 2 reported collecting follow-up tobacco use. Seven studies reported analysis of the impact of baseline tobacco use on clinical outcomes. There was significant heterogeneity in the reporting of baseline tobacco use: 7 reported never/ever status, 10 reported never/ex-smoker/current smoker status, and 4 reported measuring smoking intensity. None reported verifying smoking status or second-hand smoke exposure. Trials of lung and head and neck cancers were more likely to report baseline tobacco use than other disease sites (83% versus 6%, P < 0.001).

Conclusions: Few cancer cooperative group clinical trials report and analyze trial participants’ tobacco use. Significant heterogeneity exists in reporting tobacco use. Routine standardized collection and reporting of tobacco use at baseline and follow-up in clinical trials should be implemented to enable investigators to evaluate the impact of tobacco use on new cancer therapies.

Key words: tobacco use, clinical trials, cancer cooperative groups

INTRODUCTION

Continued smoking after a diagnosis of cancer is associated with poorer cancer outcomes across a variety of tumor sites including both tobacco- and non-tobacco-related cancers. Specifically, continued smoking worsens surgical outcomes by increasing complication rates and worsening wound healing. Among patients receiving radiation therapy, smoking can reduce treatment efficacy and increase toxicities. When patients are treated with systemic therapies, smoking can impact treatment efficacy and alter drug metabolism. Smoking can also worsen quality of life and increase the risk of recurrence and second primary malignancies. Cancer patients who continue to smoke are
also at increased risk for non-cancer related illnesses, including cardiovascular and respiratory diseases.15

With improvements in the early detection of cancer and better treatment options for many cancers, the survival prospects for patients are improving. A better understanding of how tobacco use impacts treatment outcomes is important given both the growing population of cancer survivors and new treatment options available. In clinical trials evaluating new agents or combination therapies, there may be unexpected consequences of tobacco use.16 Prior formal and informal studies identified that most oncology clinical trials do not routinely collect data on smoking history unless the tumor site is known to be associated with tobacco.16-18 Despite the lack of a clear association between tobacco use and the development of some cancers, there remains the potential for tobacco to have a negative impact on treatment outcomes. If smoking status is documented in clinical trials, it is often only at the first visit and not routinely at follow-up visits.16 This makes the evaluation of the impact of smoking on trial outcomes challenging, as some patients may quit during follow-up while others continue to smoke. Tobacco can alter the metabolism of systemic therapies, which can make the evaluation of treatment efficacy difficult if smoking status has not been assessed over time.9,16,19,20 Importantly, tobacco use could impact many trial outcomes including survival, quality of life, toxicities, and recurrence.2 In particular, as tobacco use can have a negative prognostic effect, not accounting for smoking status in clinical trials may hinder the interpretation of treatment outcomes, as some trials may only have demonstrated small differences detected between treatment arms. Therefore, the capture of smoking status should be a routine part of clinical trial data collection so that its impact on outcomes can be assessed.

Peters et al17 previously conducted a review of the National Cancer Institute (NCI) Cooperative Group Program clinical trials in the United States and identified that only 29% of trials assessed any form of tobacco use at enrollment and 22% assessed current cigarette usage at enrollment, with even fewer (5%) collecting tobacco use during the follow-up period. Most trials collecting tobacco use information were either phase III trials or trials in lung or head and neck cancer. This study focused on information collected from study protocols; however, rather than what was reported to readers in the study publication. This could further limit how much information is available to the medical community on the impact of smoking during the conduct of trials. Furthermore, the study primarily focused on trials conducted in the United States that were actively accruing patients in June 2011. Information about trials conducted by groups outside of the United States, and over a longer time period may provide a better global perspective on the extent of tobacco assessment in clinical trials.

We carried out a scoping review to better understand the reporting and analysis patterns of smoking history among cancer cooperative group clinical trials. We specifically focused on cooperative groups as these trials are undertaken by academic centers and are not directed primarily by pharmaceutical manufacturers.21 Our overall objective was to determine the frequency and format of reporting on tobacco use both at baseline and follow-up, second-hand smoke exposure, and how frequently this information was analyzed and presented in cancer cooperative group clinical trial publications.

MATERIALS AND METHODS

Search query

We conducted a systematic scoping review guided by the methodological framework articulated by Arksey and O’Malley.22 For this review, an extensive literature search was carried out for relevant studies published in English between January 2017 and October 2019 in Medline, EPub Ahead of Print and In-Process & Other Non-Indexed Citations, Embase, and Cochrane Central Register of Controlled Trials, all using the OvidSP platform. Where available, both controlled vocabulary terms and text words were utilized in the search. Where applicable, the search was limited to adults, and the following study designs: clinical trials, controlled clinical trials, randomized controlled trials, and multicenter studies. The SIGN Randomized Controlled Trials Filter and additional terms were used to ensure robustness for this topic. See Appendix S1 for the list of all search terms and search strategy used, available at https://doi.org/10.1016/j.esmoop.2022.100605.

Study inclusion and exclusion criteria

Article eligibility was first reviewed independently by two reviewers from a group of four (LE, JB, AN, SM) who screened both titles and abstracts. In cases where there was disagreement regarding eligibility, the senior author (MG) provided a third review. After title and abstract screening, full-text screens were conducted independently by two reviewers (LE and JB) and cases of disagreement in either eligibility or reason for exclusion was decided upon by the senior author (MG).

Eligible articles were original peer-reviewed studies involving cancer cooperative group clinical trials, which evaluated systemic therapy and/or radiation therapy. Eligible studies included clinical trials of any phase and disease site that involved ≥100 adult cancer patients and mentioned at least one cancer cooperative group in the title, abstract, full text, or supplementary files. In addition, eligible trials had to report at least one of the following primary or secondary endpoints: overall survival, progression-free/disease-free survival, time to progression, time to recurrence, response rate (including overall response rate, complete response, partial response), adverse events/toxicities, and/or quality of life. We included studies that were interim analyses or long-term follow-up studies if at least one of the primary or secondary endpoints were included. For the purposes of this study, we included cancer cooperative groups from all regions of the world.

Studies evaluating or comparing surgical interventions, diagnostic tests, supportive care measures only (e.g. adjunctive medications, physical activity) were excluded from the analysis. We also excluded any secondary analysis
of previously published trials (e.g. subgroup analysis, single-arm analysis, genetic analysis). Finally, review papers on trials or publications that only described the clinical trials protocol were excluded.

Data extraction and organization
The following data were extracted from each publication: title, authors, disease site, countries involved, sample size and/or actual number of patients included in analysis, patient inclusion/exclusion criteria, treatment/intervention details, trial outcomes reported in the manuscript, whether collection of baseline tobacco use information was reported in the methods or tables and how it was reported, documentation of smoking intensity and how it was quantified, reporting on the collection of follow-up smoking information, reporting of second-hand smoke exposure, how smoking status was assessed (self-report or biochemical verification). How associations between tobacco use and outcome data were recorded in manuscripts (e.g. hazard ratios along with their respective confidence intervals) was also captured.

Statistical analysis
All statistical analyses were carried out using SAS 9.4 (SAS, Cary, NC). Descriptive statistics were applied to help summarize characteristics of all included studies and compare between studies reporting and not reporting tobacco use information. As only a small number of studies collected tobacco use information, subsequent meta-analyses were not carried out. Logistic regression models were conducted to evaluate factors associated with the reporting of tobacco use in cancer cooperative group clinical trials.

RESULTS
Summary of included and excluded studies
A total of 24 975 studies were initially identified (Figure 1). Of these, 10 132 were duplicate reports/studies and were excluded and an additional 14 347 studies were excluded based on screening of the title and abstract. Among the remaining 496 manuscripts undergoing full-text review, 259 did not mention or involve a cancer cooperative group, 52 had a sample size <100 patients, 41 did not have an appropriate study design for inclusion (e.g. cohort studies, not a clinical trial), 19 did not evaluate an appropriate intervention for inclusion (e.g. surgical intervention, diagnostic test evaluation, physical activity, supportive care medications), and 13 were secondary analyses of previously published trials. Twenty-one further studies were excluded because they only described the study protocol, evaluated a non-adult patient population, did not evaluate the correct outcome, or did not have the right study design. A total of 91 studies representing 90 trials met the inclusion criteria and were included in the final analyses. Our search
found two trials that each had two manuscripts and another manuscript, in which the primary results of two similar trials were presented together. Most of the included studies were phase II or phase III clinical trials and had a sample size of <500 patients. Other characteristics of the included studies are shown in Table 1. Although all of the included studies were published after the Surgeon General’s 2014 Report, the majority of the trials were started in 2005-2010 before the report. Most studies involved systemic therapy (78%) while about one-third involved radiation therapy.

### Reporting and analysis of tobacco use in clinical trials

Among the 91 studies included, only 19 studies reported collecting tobacco use in the publication, and only two of these reported collecting any tobacco use information over the course of the trial. A summary of how tobacco use was assessed in these 19 studies is shown in Table 2 with details on each of these studies shown in Table 3. A detailed summary of all 91 studies included in this review is available by disease site in Supplementary Tables S1-S8, available at https://doi.org/10.1016/j.esmoop.2022.100605. A total of 7 studies reported smoking status as ever smoker versus never smoker status, whereas 10 studies reported smoking status as current smoker versus ex-smoker versus never smoker. We included those studies reporting smoking status only in pack-years, as lifetime smoking status (ever/never smoker) can be inferred based on pack-years. Upon review of the methodology section of these manuscripts, none formally defined smoking status or clarified the difference between current versus ex-smoker status. Only four studies reported collecting information on smoking intensity and all of them used pack-years as the measure of intensity with two reporting it as a continuous measure and two dichotomizing it at the 10 pack-year level. In the two studies that collected information on smoking status over the course of the trial, it was unclear how the information was collected and at what time intervals it was collected.

None of the manuscripts reviewed reported on how smoking status was verified. Only one study reported collecting information on nicotine dependence but did not describe what tool was used to evaluate this. Ten studies carried out analyses on the relation between tobacco use and treatment outcomes, with only seven presenting it in the results section of the manuscript; the majority of these analyses showed no significant differences in outcomes based on smoking status. None of the studies reported collecting any information on second-hand smoke exposure.

### Factors associated with the reporting of tobacco use

Table 4 summarizes the univariate and multivariate logistic regression analysis of factors associated with reporting on
| Site   | Author et al. | Year | Treatment Description | Cooperative Group | Phase | Countries | Sample size | Formal for baseline smoking status | Follow-up info | Impact of smoking on outcomes |
|--------|---------------|------|------------------------|-------------------|-------|------------|-------------|-----------------------------------|----------------|----------------------------------|
| Lung   | Atagi et al.  | 2003 | CRT with carboplatin versus RT in elderly lung cancer patients | JCOG              | III   | Japan      | 200         | Ever versus never                  | None           | Smokers had improved OS with CRT versus RT. Never smokers showed no difference between CRT and RT. Smoking did not impact grade 2+ heart or lung toxicities. |
| Lung   | Baggstrom et al. | 2008 | Sutent versus placebo after four cycles of first-line platinum-based doublet chemotherapy +/- bevacizumab in advanced NSCLC | CALGB             | III   | USA        | 210         | Never smoker, ex-smoker, current smoker | None           | Smoking status did not impact OS or PFS between arms. |
| Lung   | Ball et al.   | 2009 | SABR versus standard RT for early lung cancer | TROG              | III   | Australia, New Zealand | 101 | Never smoker, ex-smoker, current smoker | None           | Not evaluated. |
| Lung   | Bradbury et al. | 2012 | Docetaxel or pemetrexed +/- pelareorep as second line in advanced NSCLC | CCG               | II    | Canada     | 166         | Never smoker, ex-smoker, current smoker | None           | Not evaluated. |
| HNC    | Chera et al.  | 2014 | De-intensiﬁed CRT with NCI 60 Gy (with weekly cisplatin if applicable) in early HNC | CRUK              | III   | Belgium, Canada, France, Poland, Netherlands, Spain, UK | 547 | Never, <10 pack-years, >10 pack-years | None           | Pack-years not signiﬁcantly associated with time to recurrence. |
| Mesothelioma | Eberst et al. | 2008 | Cisplatin +/- pemetrexed +/- bevacizumab in advanced mesothelioma | FCIG              | III   | France     | 448         | Ever versus never                  | None           | Not evaluated. |
| Lung   | Faire-Finn et al. | 2008 | CRT with cisplatin + etoposide comparing 45Gy/30Fr versus 66Gy/33 Fr in limited SCLC | CRUK              | III   | Belgium, Canada, France, Poland, Netherlands, Spain, UK | 547 | Never smoker, ex-smoker, current smoker | None           | Not evaluated. |
| Breast | Ganz et al.   | 2000 | Doxorubicin and cyclophosphamide followed by paclitaxel +/- trastuzumab in early breast cancer | NSABP NRG         | III   | USA        | 441         | Yes versus No*                     | Yes versus No* | Smoking did not impact DASI score at follow-up. *Smoking collected during baseline PRO assessment in late follow-up. |
| HNC    | Gillison et al.| 2011 | CRT with cetuximab versus cisplatin in early HNC | RTOG              | III   | USA, Canada | 987         | 0, 0-10, >10 pack-years | None           | Patients with >10 pack-years had better 5-year OS with cisplatin compared with cetuximab. Patients with ≤10 pack-years did not show a significant difference in 5-year OS. |
| Lung   | Herbst et al. | 2009 | Carboplatin and paclitaxel with or without bevacizumab +/- cetuximab in advanced NSCLC | SWOG              | III   | USA, Mexico | 1313        | Never smoker, ex-smoker, current smoker | None           | Not evaluated. |
| Lung   | Isla et al.   | 2011 | Cisplatin with either oral vinorelbine versus oral etoposide in CRT in stage III NSCLC | SLCG              | III   | Spain      | 140         | Never smoker, ex-smoker, current smoker | None           | Possibly included in model selection, but not selected. |
| Lung   | Karampeazis et al. | 2006 | Docetaxel plus gemcitabine versus single agent gemcitabine among elderly advanced NSCLC patients | HORG              | III   | Greece     | 116         | Never smoker, ex-smoker, current smoker | None           | Not evaluated. |

Continued
tobacco use in cancer cooperative group clinical trials. There was a non-significant trend in trials involving North or Central America being more likely to report tobacco use compared with other regions of the world [29% versus 14%, odds ratio (OR) = 2.40 (0.85-6.81), P = 0.10]. Clinical trials involving either lung or head and neck cancers were more likely to report tobacco use [83% versus 5%, OR = 86.25 (17.45-426.21), P < 0.001]. Multivariate regression analysis identified that disease site was the only significant factor associated with the reporting of tobacco use. Other trial characteristics including sample size, year of publication, stage of disease, types of treatments under evaluation, and trial start year and phase were not found to be significantly associated with reporting on tobacco use (P > 0.05).

### DISCUSSION

Continuing to smoke after a diagnosis of cancer is an important clinical concern. Despite evidence to support the negative prognostic effects of smoking on cancer outcomes, less is known about how tobacco can impact treatment outcomes and adverse events. Clinical trials including those run by cancer cooperative groups may provide an opportunity to evaluate the impact of smoking on treatment-related outcomes. In our scoping review, we identified that <30% of cancer cooperative group clinical trials reported collecting any information on smoking status. Only two trials reported that information on smoking status was collected after the initial visit. There was also significant heterogeneity in the reporting of baseline smoking.
A number of factors may impede the routine collection and reporting of tobacco use in clinical trials. The first may be the perception that tobacco has little impact on clinical outcomes in trials. Previous studies and the 2014 Surgeon General’s Report demonstrate, however, that tobacco can have a powerful impact on the outcomes for many cancer types and this should be considered when evaluating clinical trial results. Other factors include the time and resource demands that would be required with the inclusion of smoking status in trial design, and perceptions that tobacco cessation may not be a viable option for many patients, despite evidence that patients not infrequently quit smoking after a cancer diagnosis and that smoking status can have negative impact on treatment outcomes.

To date, there have been few studies evaluating the frequency of assessing tobacco use in cancer clinical trials. A prior review identified that only 30% of active trials accruing in 2011 in the NCI’s Clinical Trials Cooperative Group program collected tobacco use information and <5% collected follow-up tobacco information. The majority of these trials were lung and head and neck cancer trials. Similarly, a review of the Alliance Lung Cancer Treatment Trial protocols identified that only 10 of 32 trials collected any information on smoking status, and only 6 of these trials had data that were usable for secondary analysis of the impact of tobacco on clinical outcomes. Apart from the studies included in these reviews, we were unable to identify any further cooperative group studies even amongst trials after the Surgeon General’s 2014 Report. Furthermore, most studies have only reported on what smoking status data were collected in the trial protocols and not on analyses of the impact of tobacco use on clinical outcomes. This is a missed opportunity to evaluate how tobacco may impact both prognostic and treatment-related outcomes, especially in the non-tobacco-related cancers. Furthermore, the lack of reporting of tobacco use and analysis in publications can also limit public awareness of the potential impact of tobacco on trial outcomes.

### Table 4. Summary of univariate and multivariate regression analysis results evaluating factors associated with reporting tobacco use in cancer cooperative group clinical trials

| Variable                  | Comparison                                      | Percentage of studies reporting tobacco use within each subgroup | Univariate analysis OR (95% CI) | P value | Multivariate analysis aOR (95% CI) | P value |
|---------------------------|-------------------------------------------------|------------------------------------------------------------------|---------------------------------|---------|-----------------------------------|---------|
| Year of publication       | 2016-2017 versus 2019                           | 26% Versus 21%                                                  | 1.26 (0.40-4.01)                | 0.69    | 0.98 (0.32-2.84)                  | 0.95    |
|                           | 2018 versus 2019                               | 13% Versus 21%                                                  | 0.52 (0.12-2.37)                | 0.40    | 0.90 (0.33-2.45)                  | 0.85    |
| Trial start year          | 2005-2010 versus pre-2005                      | 15% Versus 25%                                                  | 1.56 (0.38-6.38)                | 0.54    | 0.90 (0.31-2.69)                  | 0.88    |
|                           | 2011 Beyond versus pre-2005                    | 18% Versus 25%                                                  | 0.85 (0.17-4.37)                | 0.84    | 0.90 (0.31-2.69)                  | 0.88    |
| Sample size               | Per patient increase                           | —                                                               | 1.00 (0.99-1.00)                | 0.57    | 0.90 (0.31-2.69)                  | 0.88    |
| Region of world involved  | North/Central America versus not               | 29% Versus 14%                                                  | 2.40 (0.85-6.81)                | 0.10    | 0.90 (0.31-2.69)                  | 0.88    |
|                           | South America versus not                       | 100% Versus —                                                   | —                               | —       | 0.90 (0.31-2.69)                  | 0.88    |
|                           | Europe versus not                              | 19% Versus 23%                                                  | 0.77 (0.28-2.14)                | 0.61    | 0.90 (0.31-2.69)                  | 0.88    |
|                           | Africa versus not                              | 100% Versus —                                                   | —                               | —       | 0.90 (0.31-2.69)                  | 0.88    |
|                           | Asia versus not                                | 6% Versus 24%                                                   | 0.21 (0.03-1.71)                | 0.15    | 0.90 (0.31-2.69)                  | 0.88    |
|                           | Australia versus not                           | 20% Versus 21%                                                  | 0.94 (0.10-8.98)                | 0.96    | 0.90 (0.31-2.69)                  | 0.88    |
| Disease site              | Lung/head and neck versus other                | 83% Versus 6%                                                   | 86.25 (17.45-426.21)            | <0.001  | 86.25 (17.45-426.21)              | <0.001  |
| Stage of disease          | Hematology versus early                        | 0% Versus 28%                                                  | —                               | —       | 0.90 (0.31-2.69)                  | 0.88    |
|                           | Late versus early                              | 20% Versus 28%                                                  | 0.64 (0.21-1.91)                | 0.42    | 0.90 (0.31-2.69)                  | 0.88    |
| Trial phase               | II versus III                                  | 18% Versus 22%                                                  | 0.77 (0.23-2.63)                | 0.68    | 0.90 (0.31-2.69)                  | 0.88    |
| Involving radiation therapy| Yes versus no                                  | 25% Versus 19%                                                  | 1.45 (0.52-4.09)                | 0.48    | 0.90 (0.31-2.69)                  | 0.88    |
| Involving systemic therapy| Yes versus no                                  | 22% Versus 15%                                                  | 1.53 (0.31-7.59)                | 0.60    | 0.90 (0.31-2.69)                  | 0.88    |

aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

*Indicates comparisons that were not carried out due to one subgroup not having any trials within it (indicated by —).
potential barriers and considerations. First, patients may misreport their tobacco use to their care providers and biochemical testing may be required to verify smoking status. This was not carried out in most of the cancer cooperative group clinical trials included in our review.16,120,121 Biochemical testing may be challenging to implement in trials.122 Self-reported smoking status, however, is considered to be fairly accurate in many epidemiological studies.123 Despite implementing standardized collection of tobacco information in clinical trials, the reporting of this information may vary as seen in our review. Some trials report only smoking status at diagnosis or trial entry, whereas others may capture and report additional measures such as dose-intensity, quit attempts, and nicotine dependence level. Developing a common standardized way to report tobacco use in trials may be required. Furthermore, none of the trials included in this review reported second-hand smoke exposure, which may negatively impact patient outcomes and quit rates.124,125 With the recent increased prevalence of electronic cigarettes and cannabis use, these additional forms of tobacco, nicotine, and combustible exposure will also need to be assessed and evaluated in relation to cancer outcomes.

There are limitations to our study. First, we focused on reporting tobacco use in clinical trials based on their publications, but some studies may have collected this information in their protocol and not reported on it, leading to an underestimate. Reported information, however, is what readers can access to understand the effects of tobacco use on trial outcomes. Our included studies spanned a wide range of starting years which may make these results difficult to interpret. This range and variation, however, does have an advantage as it enables us to evaluate trials which were initiated over multiple time periods including before and after the Surgeon General’s Report in 2014. Third, our inclusion criteria focused on studies with ≥100 patients, which therefore excluded small early-phase trials where more detailed assessments including pharmacokinetics are likely to have been evaluated. Many early-phase studies, however, are of treatments that do not ultimately proceed to later-phase trials. Furthermore, given the strict inclusion and exclusion criteria, some trials may not have been included in our review. In addition, our review focused primarily on radiation and systemic therapy trials and did not include surgical trials. Tobacco is known to potentially negatively impact surgical outcomes3,4 however, and a future review focusing reporting of tobacco use and their analyses in surgical oncologic trials should be completed.

In conclusion, only about one-third of cancer cooperative group clinical trial publications report any tobacco use information. When reported, it was predominantly in trials involving lung or head and neck cancers. Trials reporting tobacco use information showed significant heterogeneity in how smoking status was reported, as well as variability in reporting dose-intensity measures. Most of these studies did not evaluate the impact of tobacco use on trial outcomes. Future cancer cooperative clinical trials should routinely incorporate standardized methods to assess, collect, and evaluate the impact of tobacco use on clinical outcomes.

**FUNDING**

None declared.

**DISCLOSURE**

The authors have declared no conflicts of interest.

**REFERENCES**

1. Toll BA, Brandon TH, Gritz ER, Warren GM, Herbst RS, AACR Subcommittee on Tobacco and Cancer. Assessing tobacco use by cancer patients and facilitating cessation: an American Association for Cancer Research policy statement. Clin Cancer Res. 2013;19:1941-1948.

2. U.S. Department of Health and Human Services. The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.

3. Sorensen LT. Wound healing and infection in surgery: the pathophysiological impact of smoking, smoking cessation, and nicotine replacement therapy: a systematic review. Ann Surg. 2012;255:1069-1079.

4. Sharma A, Deeb AP, Iannuzzi JC, Rickles AS, Monson JRT, Fleming FJ. Tobacco smoking and postoperative outcomes after colorectal surgery. Ann Surg. 2013;258:296-300.

5. Rugg T, Saunders MJ, Dische S. Smoking and mucosal reactions to radiotherapy. Br J Radiol. 1990;63:554-556.

6. Alsidius D, Hedelin M, Johansson KA, et al. Tobacco smoking and long-lasting symptoms from the bowel and the anal-sphincter region after radiotherapy for prostate cancer. Radiother Oncol. 2011;101:495-501.

7. Efrel PJ, Jhingran A, Bodurka DC, Levenback C, Thames H. Correlation of smoking history and other patient characteristics with major complications of pelvic radiation therapy for cervical cancer. J Clin Oncol. 2002;20:3651-3657.

8. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. 2005;353:123-132.

9. van der Bol JM, Mathijsen RH, Loos WJ, et al. Cigarette smoking and irinotecan treatment: pharmacokinetic interaction and effects on neutropaenia. J Clin Oncol. 2007;25:2719-2726.

10. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med. 2004;350:2129-2139.

11. Keizman D, Gottfried M, Ish-Shalom M, et al. Active smoking may negatively affect response rate, progression-free survival, and overall survival of patients with metastatic renal cell carcinoma treated with sunitinib. Oncologist. 2014;19:51-60.

12. Warren GW, Singh AK. Nicotine and lung cancer. J Carcinog. 2013;12:1.

13. Zhang J, Kamdar Q, Le W, Rosen GD, Upadhyay D. Nicotine induces resistance to chemotherapy by modulating mitochondrial signaling in lung cancer. Am J Respir Cell Mol Biol. 2009;40:135-146.

14. Peppeone LJ, Mustian KM, Morrow GR, et al. The effect of cigarette smoking on cancer treatment-related side effects. Oncologist. 2011;16:1784-1792.

15. Bittner N, Merrick GS, Galbreath RW, et al. Primary causes of death after permanent prostate brachytherapy. Int J Radiat Oncol Biol Phys. 2008;72:433-440.

16. Gritz ER, Dresler C, Sarna L. Smoking, the missing drug interaction in clinical trials: ignoring the obvious. Cancer Epidemiol Biomarkers Prev. 2005;14:2287-2293.
17. Peters EN, Torres E, Toll BA, et al. Tobacco assessment in actively accruing National Cancer Institute Cooperative Group Program Clinical Trials. J Clin Oncol. 2012;30:2869-2875.

18. Peters EN, Warren GW, Sloan JA, Marshall JR. Tobacco assessment in completed lung cancer treatment trials. Cancer. 2016;122:3260-3262.

19. Omenn GS, Goodman GE, Thornquist MD, et al. Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. J Natl Cancer Inst. 1996;88:1550-1559.

20. Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med. 1996;334:1150-1155.

21. Tibau A, Anguera G, Andrés-Pretel F, et al. Role of cooperative groups and funding source in clinical trials supporting guidelines for systemic therapy of breast cancer. Oncotarget. 2018;9:15061-15067.

22. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol. 2009;8:19-32.

23. Atagi S, Mizusawa J, Ishikura S, et al. Chemoradiotherapy in elderly patients with non-small-cell lung cancer: long-term follow-up of a randomized trial (JCOG0301). Clin Lung Cancer. 2018;19:e619-e627.

24. Baggstrom MQ, Socinski MA, Wang XF, et al. Maintenance sunitinib, bevacizumab, or the combination as maintenance therapy for advanced nonsquamous non-small-cell lung cancer: a randomized, double-blind, placebo-controlled phase III study-CALGB 30607 (Alliance). J Thorac Oncol. 2017;12:843-849.

25. Ball D, Mai GT, Vinod S, et al. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial. Lancet Oncol. 2019;20:494-503.

26. Bradbury PA, Morris DG, Nicholas G, et al. Canadian Cancer Trials Group (CCTG) IND211: a randomized trial of pelareorep (Reolysin) in patients with previously treated advanced or metastatic non-small cell lung cancer receiving standard salvage therapy. Lung Cancer. 2018;120:142-148.

27. Chera BS, Amdur RJ, Green R, et al. Phase II trial of de-intensified chemoradiotherapy for human papillomavirus-associated oropharyngeal squamous cell carcinoma. J Clin Oncol. 2019;37(29):2661-2669.

28. Eberst G, Anota A, Scherperelle E, et al. Health-related quality of life impact from adding bevacizumab to cisplatin-pemetrexed in malignant pleural mesothelioma in the MAPS IFT-GFPC-0701 phase III trial. Clin Cancer Res. 2019;25(19):5759-5765.

29. Falve-Finn C, Snee M, Ashcroft L, et al. Maintenance sunitinib, bevacizumab, or the combination as maintenance therapy for advanced nonsquamous non-small-cell lung cancer: results of the randomized phase II AFUGEM GERCOR clinical trial. Lung Cancer. 2017;120:142-148.

30. Ganz PA, Romond EH, Cecchini RS, et al. Long-term follow-up of cardiac function and quality of life for patients in NSABP protocol B-31/NRG oncology: a randomized trial comparing the safety and efficacy of doxorubicin and cyclophosphamide (AC) followed by paclitaxel with AC followed by paclitaxel and trastuzumab in patients with node-positive breast cancer with tumors overexpressing human epidermal growth factor receptor 2. J Clin Oncol. 2017;35:3942-3948.

31. Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. Lancet. 2019;393:40-50.

32. Herbst RS, Redman MW, Kim ES, et al. Cetuximab plus carboplatin and paclitaxel with or without bevacizumab versus carboplatin and paclitaxel with or without bevacizumab in advanced NSCLC (SWOG S0819): a randomised, phase 3 study. Lancet Oncol. 2018;19:101-114.

33. Isla D, De Las Penas R, Insa A, et al. Oral vinorelbine versus etoposide with cisplatin and chemotherapy as treatment in patients with stage III non-small cell lung cancer: a randomized phase II (RENO study). Lung Cancer. 2019;135:161-168.

34. Karampeazis A, Varvakas L, Kotsakis A, et al. Docetaxel plus gemcitabine versus gemcitabine in elderly patients with advanced non-small cell lung cancer and use of a geriatric assessment: lessons from a prematurely closed Hellenic Oncology Research Group randomized phase III study. J Geriatr Oncol. 2017;8:23-30.

35. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet. 2017;389:1011-1024.

36. Ramalingam SS, Dahlberg SE, Belani CP, et al. Pemetrexed, bevacizumab, or the combination as maintenance therapy for advanced nonsquamous non-small-cell lung cancer: ECOG-ACRIN 5508. J Clin Oncol. 2019;37:2360-2367.

37. Tao Y, Auperin A, Sire C, et al. Improved outcome by adding concurrent chemotherapy to cetuximab and radiotherapy for locally advanced head and neck carcinomas: results of the GORTEC 2007-01 phase III randomized trial. J Clin Oncol. 2018;36:3084-3090.

38. Tewari KS, Sill MW, Penson RT, et al. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). Lancet. 2017;390:1654-1663.

39. Wakelee HA, Dahlberg SE, Keller SM, et al. Adjuvant chemotherapy with or without bevacizumab in patients with resected non-small-cell lung cancer (E1505): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 2017;18:1610-1623.

40. West HL, Moon J, Wozniak AJ, et al. Paired phase II studies of erlotinib/bevacizumab for advanced bronchioloalveolar carcinoma or never smokers with advanced non-small-cell lung cancer: SWOG S0635 and S0636 trials. Clin Lung Cancer. 2018;19:84-92.

41. Xiao C, Zhang Q, Nguyen-Tan PF, et al. Quality of life and performance status from a subsidy conducted within a prospective phase 3 randomized trial of concurrent standard radiation versus accelerated radiation plus cisplatin for locally advanced head and neck carcinoma: NRG oncology RTOG 0129. Int J Radiat Oncol Biol Phys. 2017;97:667-677.

42. Alderson D, Cunningham D, Nankivell M, et al. Neoadjuvant cisplatin and fluorouracil versus epirubicin, cisplatin, and bevacitabine followed by resection in patients with oesophageal adenocarcinoma (UK MRC OEO5): an open-label, randomised phase 3 trial. Lancet Oncol. 2017;18:1249-1260.

43. Azria D, Doyen J, Larlier M, et al. Late toxicities and clinical outcome at 5 years of the ACCORD 12/0405-PRODIGE 02 trial comparing two neoadjuvant chemoradiotherapy regimens for intermediate-risk rectal cancer. Ann Oncol. 2017;28:2436-2442.

44. Bekaii-Saab TS, Ou FS, Ahn DH, et al. Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study. Lancet Oncol. 2019;20:1070-1082.

45. Charton E, Bachet JB, Hammel P, et al. Impact on health-related quality of life deterioration-free survival of a first-line therapy combining nab-paclitaxel plus either gemcitabine or simplified levocuvorin and fluorouracil for patients with metastatic pancreatic cancer: results of the randomized phase II AFUGEM GERCOR clinical trial. Cancer Med. 2019;8:5079-5088.

46. Cunningham D, Stenning SP, Smyth EC, et al. Peri-operative chemotherapy with or without bevacizumab in operable oesophago-gastric adenocarcinoma (UK Medical Research Council ST03): primary analysis results of a multicentre, open-label, randomised phase 2-3 trial. Lancet Oncol. 2017;18:357-370.

47. Hagiwara Y, Ohashi Y, Uesaka K, et al. Health-related quality of life of adjuvant chemotherapy with S-1 versus gemcitabine for resected pancreatic cancer: results from a randomised phase III trial (JAPAC 01). Eur J Cancer. 2018;83:79-88.

48. Heinrich MC, Rankin C, Blanke CD, et al. Correlation of long-term results of imatinib in advanced gastrointestinal stromal tumors with next-generation sequencing results: analysis of phase 3 SWOG intergroup trial 50033. JAMA Oncol. 2017;3:944-952.

49. Kim SY, Joo J, Kim TW, et al. A randomized phase 2 trial of consolidation chemotherapy after preoperative chemoradiation therapy versus chemoradiation therapy alone for locally advanced rectal cancer: KCSG CO 14-03. Int J Radiat Oncol Biol Phys. 2018;101:889-899.

50. Lee KW, Maeng CH, Kim TY, et al. A Phase III study to compare the efficacy and safety of paclitaxel versus irinotecan in patients with...
metastatic or recurrent gastric cancer who failed in first-line therapy (KCSG ST10-01). Oncologist. 2019;24:18-24.

51. Morizane C, Okusaka T, Mizusawa J, et al. Combination gemcitabine plus S-1 versus gemcitabine plus cisplatin for advanced/recurrent biliary tract cancer: the FUGA-BT (JCOG1113) randomized phase III clinical trial. Ann Oncol. 2019;30:1950-1958.

52. Nakayama G, Mitsuma A, Sunagawa Y, et al. Randomized phase II trial of CapOx plus bevacizumab and CapRI plus bevacizumab as first-line treatment for Japanese patients with metastatic colorectal cancer (CCOG-1201 Study). Oncologist. 2018;23:919-927.

53. Suntharalingam M, Winter K, Ison D, et al. Effect of the addition of cetuximab to paclitaxel, cisplatin, and radiotherapy for patients with esophageal cancer: the NRG oncology RTOG 0436 phase 3 randomized clinical trial. JAMA Oncol. 2017;3:1520-1528.

54. Yamada Y, Boku N, Mizusawa J, et al. Docetaxel plus cisplatin and S-1 versus cisplatin and S-1 in patients with advanced gastric cancer (JCOG1013): an open-label, phase 3, randomised controlled trial. Lancet Gastroenterol Hepatol. 2019;4:501-510.

55. Yoshida K, Kodera Y, Kochi M, et al. Addition of docetaxel to oral fluoropyrimidine improves efficacy in patients with stage III gastric cancer: interim analysis of JACCRO GC-07, a randomized controlled trial. J Clin Oncol. 2019;37:1296-1304.

56. Yoshikawa T, Terashima M, Mizusawa J, et al. Four courses versus eight courses of adjuvant S-1 for patients with stage II gastric cancer (JCOG1104 [OPAS-1]): an open-label, phase 3, non-inferiority, randomised trial. Lancet Gastroenterol Hepatol. 2019;4:208-216.

57. Churilla TM, Ballman KV, Brown PD, et al. Stereotactic radiosurgery with or without whole-brain radiation therapy for limited brain metastases: a secondary analysis of the north central cancer treatment group N0574 (Alliance) randomized controlled trial. Int J Radiat Oncol Biol Phys. 2017;99:1173-1178.

58. Ferry D, Billingham L, Jarrett H, et al. Carboplatin versus two doses of cisplatin in combination with gemcitabine in the treatment of advanced non-small-cell lung cancer: results from a British Thoracic Oncology Group randomised phase III trial. Eur J Cancer. 2017;83:302-312.

59. Bruner DW, Pugh SL, Lee WR, et al. Quality of life in patients with low-risk prostate cancer treated with hypofractionated vs conventional radiotherapy: a phase 3 randomized clinical trial. JAMA Oncol. 2019;5:664-670.

60. Carles J, Gallardo E, Domenech M, et al. Phase 2 randomized study of radiation therapy and 3-year androgen deprivation with or without concurrent weekly docetaxel in high-risk localized prostate cancer patients. Int J Radiat Oncol Biol Phys. 2019;103:344-352.

61. Duchesne GM, Woo HH, King M, et al. Health-related quality of life for immediate versus delayed-androgen-deprivation therapy in patients with asymptomatic, non-curable prostate cancer (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial. Lancet Oncol. 2017;18:1192-1201.

62. Lukka HR, Pugh SL, Bruner DW, et al. Patient reported outcomes in NRG oncology RTOG 0938, evaluating two ultrahypofractionated regimens for prostate cancer. Int J Radiat Oncol Biol Phys. 2018;102:287-295.

63. Roach M, Moughan J, Lawton CAF, et al. Sequence of hormonal therapy and radiotherapy field size in unfavourable, localised prostate cancer (NRG/RTOG 9413): long-term results of a randomised, phase 3 trial. Lancet Oncol. 2018;19:1504-1515.

64. Rosenthal SA, Hu C, Sartor O, et al. Effect of chemotherapy with docetaxel with or without bevacizumab and carboplatin versus placebo plus bevacizumab and paclitaxel in patients with advanced gastric cancer: the phase 3 randomized controlled trial. Ann Oncol. 2019;29:1159-1168.

65. Chekerov R, Hilpert F, Mahner S, et al. Sorafenib plus topotecan versus placebo plus topotecan for platinum-resistant ovarian cancer (TRIAS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol. 2018;19:1247-1258.

66. Del Campo JM, Matulonius UA, Mabasser S, et al. Niraparib maintenance therapy in patients with recurrent ovarian cancer after a partial response to the last platinum-based chemotherapy in the ENGOT-OV16/NOVA trial. J Clin Oncol. 2019;37(32):2968-2973.

67. Klopp AH, Yeung AR, Deshmukh S, et al. Patient-reported toxicity during pelvic intensity-modulated radiation therapy: NRG Oncology-RTOG 1203. J Clin Oncol. 2018;36:2538-2544.

68. Matei D, Filicic V, Randall ME, et al. Adjuvant chemotherapy plus radiation for locally advanced endometrial cancer. N Engl J Med. 2019;380:2317-2326.

69. Matulonius UA, Sill MW, Makker V, et al. A randomized phase II study of capecitabine versus weekly paclitaxel in the treatment of persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer: an NRG Oncology/Gynecologic Oncology Group study. Gynecol Oncol. 2019;152:548-553.

70. Monk BJ, Brady MF, Aghajanian C, et al. A phase 2, randomized, double-blind, placebo-controlled study of chemo-immunotherapy combination using motolimod with pegylated liposomal doxorubicin in recurrent or persistent ovarian cancer: a Gynecologic Oncology Group partners study. Ann Oncol. 2017;28:996-1004.

71. Piccirillo MC, Scambia G, Bologna A, et al. Quality-of-life analysis of the MITO-8, MaNGO, BOG-Ov1, AGO-Ovar2.16, ENGOT-Ov1, GCIG study comparing platinum-based versus non-platinum-based chemotherapy in patients with partially platinum-sensitive recurrent ovarian cancer. Ann Oncol. 2018;29:1139-1149.

72. Pignata S, Scambia G, Bologna A, et al. Randomized controlled trial testing the efficacy of platinum-free interval prolongation in advanced ovarian cancer: the MITO-8, MaNGO, BOG-Ov1, AGO-Ovar2.16, ENGOT-Ov1, GCIG Study. J Clin Oncol. 2017;35:3347-3353.

73. Spirtos NM, Enserro D, Homesley HD, et al. The addition of paclitaxel to doxorubicin and cisplatin and volume-directed radiation does not improve overall survival (OS) or long-term recurrence-free survival (RFS) in advanced endometrial cancer (EC): a randomized phase III NRG/Gynecologic Oncology Group (GOG) study. Gynecol Oncol. 2019;154:13-21.

74. Kodaira T, Kagami Y, Shibata T, et al. Results of a multi-institutional, randomized, non-inferiority, phase III trial of accelerated fractionation versus standard fractionation in radiation therapy for T1-2N0M0 glottic cancer: Japan Clinical Oncology Group Study (JCOG0701). Ann Oncol. 2018;29:992-997.

75. Bassan R, Intermesoli T, Masciulli A, et al. Randomized trial comparing standard vs sequential high-dose chemotherapy for inducing early CR in adult AML. Blood Adv. 2019;3:1103-1117.

76. Borchmann P, Haverkamp H, Lohri A, et al. Progression-free survival of early interim PET-positive patients with advanced stage Hodgkin’s lymphoma treated with BEACOPP escalated alone or in combination with rituximab (HD18): an open-label, international, randomised phase 3 study by the German Hodgkin Study Group. Lancet Oncol. 2017;18:454-463.

77. Borchmann P, Goergen H, Kobe C, et al. PET-guided treatment in patients with advanced-stage Hodgkin’s lymphoma (HD18): final results of a open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. Lancet. 2018;390:2790-2802.

78. Dartigeas C, Van Den Neste E, Leger J, et al. Rituximab maintenance versus observation following abbreviated induction with chemo-immunotherapy in elderly patients with previously untreated chronic lymphocytic leukaemia (CALL 2007 SA): an open-label, randomised phase 3 study. Lancet Haematol. 2018;5:e82-e94.

79. Durie BG, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG 0777): a randomised, open-label, phase 3 trial. Lancet. 2017;389:519-527.

80. Eichenauer DA, Plutschow A, Kreissl S, et al. Incorporation of brentuximab vedotin into first-line treatment of advanced classical Hodgkin’s lymphoma: final analysis of a phase 2 randomised trial by the German Hodgkin Study Group. Lancet Oncol. 2017;18:1680-1687.

81. Ferreri AJM, Cwynarski K, Pulszynski E, et al. Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose methotrexate-based chemo-immunotherapy in patients with primary CNS lymphoma: results of the second randomisation of the International Extranodal Lymphoma Study Group-32 phase 2 trial. Lancet Haematol. 2017;4:e510-e523.
82. Fuchs M, Goerger H, Kobe C, et al. Postiron emission tomography-guided treatment in early-stage favorable Hodgkin lymphoma: final results of the international, randomized phase III HD16 trial by the German Hodgkin Study Group. J Clin Oncol. 2019;37(31):2833-2845.

83. Holstein SA, Jung SH, Richardson PG, et al. Updated analysis of CALGB (Alliance) 100104 assessing lenalidomide versus placebo maintenance after single autologous stem-cell transplantation for multiple myeloma: a randomised, double-blind, phase 3 trial. Lancet Haematol. 2017;4:e431-e442.

84. MacManus M, Fisher R, Roos D, et al. Randomized trial of systemic therapy after involved-field radiotherapy in patients with early-stage follicular lymphoma: TROG 99.03. J Clin Oncol. 2018;36:918-2925.

85. Platzecker U, Avvisati G, Ciconi L, et al. Improved outcomes with retinoic acid and arsenic trioxide compared with retinoic acid and chemotherapy in non-high-risk acute promyelocytic leukemia: final results of the randomized Italian-German APL0406 trial. J Clin Oncol. 2017;35:605-612.

86. Sakura T, Hayakawa F, Sugii A, et al. High-dose methotrexate therapy significantly improved survival of adult acute lymphoblastic leukemia: a phase III study by JALSG. Leukemia. 2018;32:625-632.

87. Watanabe T, Tobinai K, Wakabayashi M, et al. Outcomes after R-CHOP in patients with newly diagnosed advanced follicular lymphoma: a 10-year follow-up analysis of the JCOG0203 trial. Lancet Haematol. 2018;5:e520-e531.

88. Xu PP, Fu D, Li JY, et al. Anthracycline dose optimisation in patients with diffuse large B-cell lymphoma: a multicentre, phase 3, randomised, controlled trial. Lancet Haematol. 2019;6:e328-e337.

89. Bhattacharya IS, Hawliden JS, Kirby AM, et al. Patient-reported outcomes over 5 years after whole- or partial-breast radiotherapy: longitudinal analysis of the import low (CRUK/06/003) phase III randomized controlled trial. J Clin Oncol. 2019;37:305-317.

90. Cameron D, Morden JP, Canney P, et al. Accelerated versus standard epirubicin followed by cyclophosphamide, methotrexate, and fluorouracil or capcitabine as adjuvant therapy for breast cancer in the randomized UK TACT2 trial (CRUK/05/19): a multicentre, phase 3, open-label, randomised, controlled trial. Lancet Oncol. 2017;18:929-945.

91. Campone M, Lacroix-Triki M, Roca L, et al. UCBG 2-08: 5-year final analysis of the JCOG0203 trial. J Clin Oncol. 2017;35:805-814.

92. Coles CE, Griffin CL, Kirby AM, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled trial. Lancet. 2019;394:1048-1060.

93. Earl HM, Hiller L, Howard HC, et al. Addition of gemcitabine to paclitaxel, epirubicin, and cyclophosphamide adjuvant chemotherapy for women with early-stage breast cancer (tAnGo): 10-year follow-up of an open-label, randomised, controlled, phase 3 trial. Lancet. 2019;394:1048-1060.

94. Flora O, Nitz U, Liedtke C, et al. Comparison of neoadjuvant nab-paclitaxel-carboplatin versus nab-paclitaxel-gemcitabine in triple-negative breast cancer: randomized WSG-ADAPT-TN trial results. J Natl Cancer Inst. 2018;110:628-637.

95. Gniant M, Pfeifer G, Steger GG, et al. Adjuvant denosumab in postmenopausal patients with hormone receptor-positive breast cancer (ABC08-18): disease-free survival results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019;20:339-351.

96. Kim JY, Park S, Im SA, et al. Quality of life outcomes including neuropathy-associated scale from a phase II, multicenter, randomized trial of eribulin plus gemcitabine versus paclitaxel plus gemcitabine as first-line chemotherapy for HER2-negative metastatic breast cancer: Korean Cancer Study Group Trial (KCSG BR13-11). Cancer Commun. 2018;19:29-39.

97. Lindman H, Andersson M, Ahlgren J, et al. A randomised study of tailored toxicity-based dosage of fluorouracil-epirubicin-cyclophosphamide chemotherapy for early breast cancer (SBG 2000-1). Eur J Cancer. 2018;94:79-86.

98. Mamounas EP, Bandos H, Lembersky BC, et al. Use of letrozole after aromatase inhibitor-based therapy in postmenopausal breast cancer (NRC Oncology/NSABP B-42): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019;20:88-99.

99. Miller KD, O’Neill A, Gradishar W, et al. Double-blind phase III trial of adjuvant chemotherapy with and without bevacizumab in patients with lymph node-positive and high-risk lymph node-negative breast cancer (E5103). J Clin Oncol. 2018;36:2621-2629.

100. Schaefer R, Strnad V, Polgar C, et al. Quality-of-life results for accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation in early breast cancer after breast-conserving surgery (GEC-ESTRO): 5-year results of a randomised, phase 3 trial. Lancet Oncol. 2018;19:834-844.

101. Wagner U, Zhao F, Goss PE, et al. Patient-reported predictors of early treatment discontinuation: treatment-related symptoms and health-related quality of life among postmenopausal women with primary breast cancer randomized to anastrozole or exemestane on NCIC Clinical Trials Group (CCTG) MA-27 (E1203). Breast Cancer Res Treat. 2018;169:537-548.

102. Brown PD, Salman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCTCT N107C/EC:3): a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol. 2017;18:1049-1060.

103. Coens C, Suci S, Chiarion-Sileni V, et al. Health-related quality of life with adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): secondary outcomes of a multinational, randomised, double-blind, phase 3 trial. Lancet Oncol. 2017;18:393-403.

104. Dirksen U, Brennan B, Le Deley MC, et al. High-dose chemotherapy compared with standard chemotherapy and lung radiation in Ewing Sarcoma with pulmonary metastases: results of the European Ewing Tumour Working Initiative of National Groups, 99 trial and EWING 2008. J Clin Oncol. 2019;37(34):3192-3202.

105. Gilbert MR, Pugh SL, Aldape K, et al. NRG oncology RTOG 0625: a randomized phase II trial of bevacizumab with either irinotecan or dose-dense temozolomide in recurrent glioblastoma. J Neurooncol. 2017;131:193-199.

106. Gronchi A, Ferrari S, Quagliuolo V, et al. Histotype-tailored neo-adjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. Lancet. 2019;378:812-822.

107. Herrlinger U, Tzaridis T, Mack F, et al. Lomustine-temozolomide combination therapy versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with methylated MGMT promoter (CEtEG/NOA-09): a randomised, open-label, phase 3 trial. Lancet. 2019;393:678-688.

108. Kayama T, Sato S, Sakurada K, et al. Effects of surgery with salvage stereotactic radiosurgery versus surgery with whole-brain radiation therapy in patients with one to four brain metastases (JCOG0504): A phase III, noninferiority, randomized controlled trial. J Clin Oncol. 2018;36:3282-3289.

109. Lieberman FS, Wang M, Robins HI, et al. Phase 2 study of radiation therapy plus low-dose temozolomide followed by temozolomide and irinotecan for glioblastoma: NRG Oncology RTOG trial 0420. Int J Radiat Oncol Biol Phys. 2019;103:878-886.

110. van den Bent MJ, Baumbert B, Erridge SC, et al. Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: a phase 3, randomised, open-label intergroup study. Lancet. 2017;390:1645-1653.

111. van den Bent MJ, Klein M, Smits M, et al. Bevacizumab and temozolomide in patients with first recurrence of WHO grade II and III glioma, without 1p/19q co-deletion (TAVAREC): a randomised controlled phase 2 EORTC trial. Lancet Oncol. 2018;19:1170-1179.
113. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361:947-957.

114. Eng L, Liu SY, Zhang Q, et al. Cancer patient attitudes and preferences towards smoking status assessment. *J Clin Oncol*. 2018;36. 110-110.

115. Warren GW, Marshall JR, Cummings KM, et al. Practice patterns and perceptions of thoracic oncology providers on tobacco use and cessation in cancer patients. *J Thorac Oncol*. 2013;8:543-548.

116. Land SR, Warren GW, Crafts JL, et al. Cognitive testing of tobacco use items for administration to patients with cancer and cancer survivors in clinical research. *Cancer*. 2016;122:1728-1734.

117. Land SR, Toll BA, Moinpour CM, et al. Research priorities, measures, and recommendations for assessment of tobacco use in clinical cancer research. *Clin Cancer Res*. 2016;22:1907-1913.

118. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378:113-125.

119. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078-2092.

120. Sarna L, Padilla G, Holmes C, Tashkin D, Brecht ML, Evangelista L. Quality of life of long-term survivors of non-small-cell lung cancer. *J Clin Oncol*. 2002;20:2920-2929.

121. Khuri FR, Kim ES, Lee JJ, et al. The impact of smoking status, disease stage, and index tumor site on second primary tumor incidence and tumor recurrence in the head and neck retinoid chemoprevention trial. *Cancer Epidemiol Biomarkers Prev*. 2001;10:823-829.

122. Glasgow RE, Mullooly JP, Vogt TM, et al. Biochemical validation of smoking status: pros, cons, and data from four low-intensity intervention trials. *Addict Behav*. 1993;18:511-527.

123. Patrick DL, Cheadle A, Thompson DC, Diehr P, Koepsell T, Kinne S. The validity of self-reported smoking: a review and meta-analysis. *Am J Public Health*. 1994;84:1086-1093.

124. Eng L, Su J, Qiu X, et al. Second-hand smoke as a predictor of smoking cessation among lung cancer survivors. *J Clin Oncol*. 2014;32:564-570.

125. Idris S, Baqays A, Isaac A, et al. The effect of second hand smoke in patients with squamous cell carcinoma of the head and neck. *J Otolaryngol Head Neck Surg*. 2019;48:33.