Standard-of-care systemic therapy with or without stereotactic body radiotherapy in patients with oligoprogressive breast cancer or non-small-cell lung cancer (Consolidative Use of Radiotherapy to Block [CURB] oligoprogression): an open-label, randomised, controlled, phase 2 study

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Summary

Background Most patients with metastatic cancer eventually develop resistance to systemic therapy, with some having limited disease progression (ie, oligoprogression). We aimed to assess whether stereotactic body radiotherapy (SBRT) targeting oligoprogressive sites could improve patient outcomes.

Methods We did a phase 2, open-label, randomised controlled trial of SBRT in patients with oligoprogressive metastatic breast cancer or non-small-cell lung cancer (NSCLC) after having received at least first-line systemic therapy, with oligoprogression defined as five or less progressive lesions on PET-CT or CT. Patients aged 18 years or older were enrolled from a tertiary cancer centre in New York, NY, USA, and six affiliated regional centres in the states of New York and New Jersey, with a 1:1 randomisation between standard of care (standard-of-care group) and SBRT plus standard of care (SBRT group). Randomisation was done with a computer-based algorithm with stratification by number of progressive sites of metastasis, receptor or driver genetic alteration status, primary site, and type of systemic therapy previously received. Patients and investigators were not masked to treatment allocation. The primary endpoint was progression-free survival, measured up to 12 months. We did a prespecified subgroup analysis of the primary endpoint by disease site. All analyses were done in the intention-to-treat population. The study is registered with ClinicalTrials.gov, NCT03808662, and is complete.

Findings From Jan 1, 2019, to July 31, 2021, 106 patients were randomly assigned to standard of care (n=51; 23 patients with breast cancer and 28 patients with NSCLC) or SBRT plus standard of care (n=55; 24 patients with breast cancer and 31 patients with NSCLC). 16 (34%) of 47 patients with breast cancer had triple-negative disease, and 51 (86%) of 59 patients with NSCLC had no actionable driver mutation. The study was closed to accrual before reaching the targeted sample size, after the primary efficacy endpoint was met during a preplanned interim analysis. The median follow-up was 11·6 months for patients in the standard-of-care group and 12·1 months for patients in the SBRT group. The median progression-free survival was 3·2 months (95% CI 2·0–4·5) for patients in the standard-of-care group versus 7·2 months (4·5–10·0) for patients in the SBRT group (hazard ratio [HR] 0·53, 95% CI 0·35–0·81; p=0·0035). The median progression-free survival was higher for patients with NSCLC in the SBRT group than for those with NSCLC in the standard-of-care group (10·0 months [7·2–not reached] *vs* 2·2 months [95% CI 2·0–4·5]; HR 0·41, 95% CI 0·22–0·75; p=0·0039), but no difference was found for patients with breast cancer (4·4 months [2·5–8·7] *vs* 4·2 months [1·8–5·5]; 0·78, 0·43–1·43; p=0·43). Grade 2 or worse adverse events occurred in 21 (41%) patients in the standard-of-care group and 34 (62%) patients in the SBRT group. Nine (16%) patients in the SBRT group had grade 2 or worse toxicities related to SBRT, including gastrointestinal reflux disease, pain exacerbation, radiation pneumonitis, brachial plexopathy, and low blood counts.

Interpretation The trial showed that progression-free survival was increased in the SBRT plus standard-of-care group compared with standard of care only. Oligoprogression in patients with metastatic NSCLC could be effectively treated with SBRT plus standard of care, leading to more than a four-times increase in progression-free survival compared with standard of care only. By contrast, no benefit was observed in patients with oligoprogressive breast cancer. Further studies to validate these findings and understand the differential benefits are warranted.

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See Online for appendix

Introduction

The predominant paradigm for treating metastatic cancer is cycling through different systemic therapies, with local therapy typically reserved for palliation of symptoms. Almost three decades ago, Hellman and Weichselbaum introduced the concept of oligometastatic disease, which falls between localised disease and widespread dissemination, and is characterised by a small number of metastatic sites.[1] Although historically, locally ablative therapies, such as surgery, radiation, and radiofrequency ablation, have been used for oligometastatic colorectal and other cancers, their clinical efficacy and acceptance varied.[2,3] Regardless, there is burgeoning interest in using locally ablative therapy in patients with a limited burden of metastatic disease—ie, oligometastasis.

Several prospective randomised clinical trials have shown that ablative radiotherapy in patients with oligometastatic cancer can improve progression-free survival and overall survival.[4–9] In SABR-COMET, patients who had up to five metastases from any solid tumours were randomly assigned to standard systemic therapy versus standard systemic therapy plus stereotactic ablative radiotherapy to all metastatic lesions.[8] The study showed a 22-month improvement in overall survival with the addition of ablative radiotherapy.[8] Similarly, a phase 2 randomised trial of patients with oligometastatic non-small-cell lung cancer (NSCLC) showed that the addition of local consolidative therapy (ie, surgery or radiation) to all metastatic sites improved progression-free survival and overall survival compared with standard-of-care systemic therapy alone.[9]

Although ablative radiotherapy has shown promise in treating oligometastases, its effectiveness in managing progressive or widespread metastatic disease remains unclear. Systemic therapies still constitute the mainstay of treatment; however, an unavoidable development of resistance to these therapies usually occurs over time. For example, patients with NSCLC without targetable mutations treated with first-line chemoimmunotherapy have a median response of 1–2 years before disease progression, partly due to acquired mutations in genes essential to immune regulatory functions or pathways.[10] Similarly, patients with oestrogen receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer treated with first-line CDK4 and CDK6 inhibitors and endocrine therapy can have initial disease control followed by acquired resistance to these cell cycle inhibitors through numerous pathways.[11]

Two major patterns of progression after initial response to systemic therapy have been reported: systemic progression and oligoprogression.[12] Systemic progression

Research in context

Evidence before this study

Metastasis-directed therapy has been shown to increase survival in patients with cancer and limited metastatic disease burden—ie, oligometastasis. However, its benefit is unclear in the context of oligoprogression, where patients with extensive metastatic disease on systemic therapy manifest primarily stable disease except for progression at a few sites. We searched PubMed from Jan 1, 2000, to May 31, 2023, for articles in English on the use of ablative radiotherapy for patients with oligoprogressive cancer. We used the following search terms without any further restrictions: ("oligoprogression"[All Fields] OR "oligoprogressive"[All Fields]) AND ("cancers"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]) AND ("radiotherapy"[MeSH Terms] OR "radiotherapy"[All Fields] OR "radiotherapies"[All Fields] OR "radiotherapy"[MeSH Subheading] OR "radiotherapies"[All Fields]). The search yielded 276 articles, including guidelines, systematic reviews, and retrospective case series. We did not find any prospective randomised clinical trials.

Added value of this study

To our knowledge, this study is the first phase 2 randomised controlled trial of stereotactic body radiotherapy (SBRT) in patients with oligoprogressive metastatic breast cancer or non-small-cell lung cancer (NSCLC). We found that locally ablative radiotherapy increased progression-free survival for patients with oligoprogressive cancer compared with standard of care. The significant benefit of SBRT was seen only in patients with NSCLC, showing more than a four-times increase in median progression-free survival compared with standard of care. No progression-free survival benefit was observed in patients with oligoprogressive breast cancer. Analyses of paired pre-randomisation and post-randomisation blood samples showed that radiotherapy led to changes in circulating tumour DNA metrics in patients with NSCLC, but not in patients with breast cancer.

Implications of all the available evidence

This study, together with published literature, supports the identification of oligoprogression in patients with metastatic NSCLC, which could be effectively treated with SBRT, distinct from the systemic progression seen in patients with breast cancer. The disseminated progression of breast cancer poses a challenge for identifying and effectively treating an oligoprogressive disease. To validate the efficacy of ablative radiotherapy in patients with oligoprogressive NSCLC, further research in a well defined patient population is required through a phase 3 trial.

involves the widespread growth of resistant disease throughout the body, often with the development of new lesions. By contrast, oligoprogression is characterised by localised progression of a few metastatic lesions while the disease remains controlled or stable in other areas of the body.[13] Oligoprogression arises from clonal heterogeneity and tumour evolution, where a few progressive lesions are driven by resistant clones not substantially present in other metastatic sites; it can occur in patients with oligometastatic cancer or with widespread metastatic or polymetastatic disease.[14,15] As a more recently described term, oligoprogressive disease does not have a universally accepted definition and remains a complex and not fully understood concept, with most studies using an arbitrary cutoff of three to five progressive lesions.[13,15] Selective local therapy of oligoprogressive sites aims to prolong disease control of an otherwise effective systemic therapy, since the non-progressive widespread disease is not comprehensively irradiated. By contrast, local ablative therapy for oligometastatic disease aims to achieve durable cancer remission by treating all disease sites.

Randomised controlled trials investigating the clinical impact of local ablative therapy in patients with oligoprogressive disease have not been published yet. Considering the aforementioned success of ablative radiotherapy for oligometastatic disease and advances elucidating the role of tumour heterogeneity in resistance to therapy, we hypothesised that ablative radiotherapy could benefit patients with oligoprogressive metastatic cancer. In this Article, we report on the findings from a randomised, prospective, phase 2 study assessing the benefit of ablative radiotherapy in the form of stereotactic body radiotherapy (SBRT) for oligoprogressive metastatic cancer, focusing specifically on patients with two of the most common solid tumours—breast cancer and NSCLC. As an exploratory objective, we also assessed possible changes in cell-free DNA because liquid biomarkers have been shown to be associated with prognosis and treatment outcomes.[16]

Methods

Study design

This study is a phase 2, open-label, randomised controlled trial of SBRT versus no SBRT in patients with oligoprogressive metastatic breast cancer or NSCLC. Patients were recruited from a tertiary cancer centre in New York, NY, USA, and its affiliated six regional care centres in the states of New York and New Jersey. The study was approved by the institutional review board of the Memorial Sloan Kettering Cancer Center (New York, NY, USA) and all patients provided written informed consent. The trial protocol can be found in the appendix (pp 15–51).

Patients

The eligibility criteria included: (1) patient's age of 18 years or older; (2) patient's willingness and ability to provide informed consent; (3) metastatic disease detected on imaging and histologically confirmed breast cancer or NSCLC; (4) receipt of at least first-line systemic therapy, including maintenance therapies; (5) extracranial oligoprogression, defined as having progression in up to five individual lesions according to either the Response Evaluation Criteria in Solid Tumours (RECIST) or the PET Response Criteria in Solid Tumours (PERCIST); and (6) potential for all sites of oligoprogression to be safely treated. Patients with brain metastases could receive standard-of-care brain radiation (either whole brain radiotherapy or stereotactic radiotherapy) before enrolment.

The exclusion criteria included pregnancy, leptomeningeal disease, and serious medical comorbidities precluding radiotherapy. Patients who had previously received any form of radiotherapy were eligible to enrol in the study; however, re-irradiation to the same tumour location was not allowed. Additional inclusion and exclusion criteria are given in the appendix (pp 28–30; pp 14–16 of the protocol).

All patients were assessed by screening evaluations to determine eligibility within 28 days before randomisation. Permitted initial staging imaging methods were CT, PET-CT, or MRI (or any combination thereof) of the brain, neck, chest, abdomen, pelvis, or all other known sites of disease. The potential eligibility of patients was reviewed by study radiologists to confirm eligibility for study inclusion. The type of scans done were at the discretion of the treating physician; the baseline radiological assessment chosen determined the approach used for reassessment of disease on study. Sex information was self-reported by the study participants at their first hospital encounter and recorded in their electronic health record.

Randomisation and masking

A computer-based algorithm randomly assigned patients (1:1) to one of the two following groups: in one group, patients received SBRT to the oligoprogressive sites and standard-of-care systemic therapy per physician's discretion (henceforth referred to as SBRT group); in the other group, patients received standard-of-care systemic therapy per physician's discretion but not SBRT (henceforth referred to as standard-of-care group). Patients were stratified on the basis of four stratification factors: number of oligoprogressive sites of metastasis (one *vs* two to five); receptor or driver genetic alteration status (absence or presence of *EGFR, ALK,* or *ROS* genetic alterations for patients with NSCLC and oestrogen receptor-positive or oestrogen receptor-negative status for patients with breast cancer); primary site; and type of systemic therapy received thus far (immunotherapy *vs* other). Patients who had received immunotherapy at any time were stratified as immuno-therapy regardless of other systemic therapy. Patients who had switched their systemic therapy at the time of oligoprogression or immediately after randomisation but before the first

follow-up were classified as having changed their systemic therapy at enrolment. Patients and investigators were not masked to treatment allocation.

Procedures

Radiotherapy dose was determined by the treating radiation oncologist on the basis of clinical parameter considerations, including tumour size and location. In most instances, regimens ranged from 27–30 Gy in three fractions to 30–50 Gy in five fractions. Other fractionation schemes were used infrequently, typically in patients whose lesions were in a location deemed unsafe to have the suggested radiation doses due to nearby organs at risk. No rigid tumour size cutoff for SBRT was set; however, typically, the lesion's diameter should be less than 4 cm. Detailed radiotherapy guidelines are outlined in the appendix (pp 33–35; pp 19–21 of the protocol). For patients in both the standard-of-care and SBRT groups, subsequent palliative radiotherapy could be considered if clinically warranted.

Baseline assessments included medical history, quality-of-life questionnaires (the European Organisation for Research and Treatment of Cancer quality-of-life questionnaire core 30[17] and the Common Terminology Criteria for Adverse Events [CTCAE; version 4.0]), physical examination, vital signs, performance status, and imaging (as described in the previous sections). The first follow-up assessment occurred at 8 weeks after randomisation (with an allowed time window of 2 weeks before or after 8 weeks), then every 12 weeks (with a 2-week time window before or after) until 12 months after randomisation. Before each visit, a restaging imaging evaluation was completed. The same imaging method at baseline was used for subsequent evaluations, unless an alternative method was clinically indicated. The treating physician could schedule more frequent follow-up visits between research visits if needed. All initial and follow-up imaging studies were reviewed by one of the three dedicated study radiologists to examine progression status according to predefined RECIST or PERCIST criteria. At each visit, patients underwent a focused history and physical examination, vital signs measurement, and adverse event assessment, by use of CTCAE. Quality-of-life questionnaires were timed with research visits. Additionally, each patient provided research blood samples at baseline and first follow-up for exploratory cell-free DNA analysis, and one more blood sample at the time of disease progression (if it occurred).

Circulating cell-free DNA was extracted from collected blood samples and analysed for somatic tumour circulating tumour DNA (ctDNA) alterations by Memorial Sloan Kettering–Analysis of Circulating cell-free DNA to Examine Somatic Status (MSK-ACCESS), a next-generation sequencing assay for the detection of somatic ctDNA alterations in 129 genes.[18] The assay has a 92% sensitivity for calling mutations with a 0·5% or higher allele fraction without a priori tumour mutation profiling, and 99% sensitivity if a priori mutation profiling is performed. An allele fraction is the number of mutated reads divided by the sum of wild-type and mutated reads (appendix p 3). We computed a cell-free DNA-based metric estimating ctDNA content in the paired blood samples. Briefly, mutations detected in at least one timepoint were genotyped in both timepoints to obtain their allele fractions. These mutations were then annotated using OncoKB[19] to identify known hotspot and oncogenic mutations in key cancer genes involved in breast cancer and NSCLC. If known hotspot or oncogenic mutations were present, the timepoint with higher geometric mean of allele fractions for these mutations was selected for determining clonal mutations. If no hotspot or oncogenic mutations were identified, then the timepoint with higher geometric mean of allele fraction for all the bona fide mutations was selected after filtering out known artifacts from the MSK-ACCESS assay, such as mutations that strongly associated with clonal haematopoiesis (known as clonal haematopoiesis of indeterminate potential mutations). Within the selected timepoint, clonal mutations were defined as those with allele fraction of 0·3 or higher of the mutation with the highest allele fraction. This definition served as an approximate filter to eliminate mutations that were less likely to be clonal and more likely to be subclonal. Both are types of somatic mutations. The geometric mean of these mutations was taken and multiplied by 2 with the assumption of one mutant copy and one normal copy. The choice of using the geometric mean rather than the arithmetic mean was made to lessen the effect of outliers in the chosen set of mutations. For a subset of patients with paired blood samples who also had tissue sequencing data from MSK-IMPACT (Mutation Profiling of Actionable Cancer Targets),[20] we computed tumour-informed ctDNA fraction on the basis of a previously described approach[21] and found that tumour-informed ctDNA fraction and the geometric mean of clonal somatic mutation allele fraction show satisfactory correlation (appendix p 11). Given that the inference of gene copy number de novo from cell-free DNA is fraught with difficulties due to low ctDNA content, we devised a cell-free DNA-based method to estimate ctDNA content similarly to what was done in previous work.[21] This complementary approach was applied to 23 patients with breast cancer and 17 patients with NSCLC with available tissue sequencing data (appendix p 4). For these 40 patients, ctDNA fraction was calculated in a tumour-informed way by using clonal driver mutations and copy numbers from MSK-IMPACT tissue sequencing for the same patient essentially as previously described.[22] For one patient, we had sequencing results from tissue using a different assay (AmpliSeq; Illumina, San Diego, CA, USA) instead of MSK-IMPACT and the copy number for the driver *TP53* mutation was inferred from the allele fractions and typical *TP53* copy number states in lung cancer.

Outcomes

The primary endpoint was progression-free survival, measured up to 12 months, for patients in the standard-of-care and SBRT groups, defined as the time from random assignment to systemic disease progression. Secondary outcomes were overall survival in the entire cohort and by disease group, defined as the time from random assignment to death or last follow-up; time to initiation of a new systemic therapy after the initial change of systemic therapy or no change at the time of enrolment, in the entire cohort and by disease site; toxicity of SBRT, measured by assessing adverse events according to the CTCAE criteria and with treatment-related adverse events defined by the treating physician; patient's quality of life, assessed by use of questionnaires; and progression-free survival by disease site—ie, for patients with breast cancer and for those with NSCLC in the standard-of-care and SBRT groups. As an exploratory objective, we also examined the mutational profiles of the tumours and paired blood samples collected at baseline and follow-up to assess possible changes in cell-free DNA.

Statistical analysis

For the sample size calculation, we assumed that the standard-of-care therapy had a 6-month progression-free survival of 40% for patients with oligoprogressive breast cancer and a 6-month progression-free survival of 20% for patients with oligoprogressive NSCLC. We anticipated approximately equal enrolment of patients with breast cancer and patients with NSCLC. Thus, the collective 6-month progression-free survival was assumed to be 30% for patients in the standard-of-care group and we anticipated the addition of SBRT to increase progression-free survival to 45% at 6 months. A one-sided two-sample stratified log-rank test was used by assuming exponential distributions on time to progression, 10% dropout rate per year for either group, and uniform accrual. With an α of 0·05, 160 patients (80 patients per group) were required to achieve a power of 0·80 in detecting such a difference in progression-free survival, with 132 expected events under alternative hypothesis. We expected to enrol these 160 patients in 3 years with a minimum of a 1-year follow-up. One interim analysis (at the halfway point of the study) and a final analysis were planned at equal intervals. The difference would be declared significant (ie, boundary for success) if the p value was less than 0·006 in the interim analysis and less than 0·048 in the final analysis using the Lan-DeMets spending function with an O'Brien-Fleming boundary and would be declared negative if the p value was 0·492 or larger in the interim analysis or 0·048 or larger in the final analysis. Enrolment to this study was stopped at the first planned interim analysis because the progression-free survival difference exceeded the predefined statistical boundary for success.

The analysis was intention to treat for all endpoints. Continuous variables were described using median and ranges, and categorical variables were described using frequency and percentages. Progression-free survival, overall survival, and time to initiation of a new systemic therapy were evaluated using the Kaplan-Meier method and log-rank statistics. Proportional hazards for the covariates of interest were assessed, and those that did not violate the assumption were evaluated in univariable Cox models. Stratified Cox multivariable models were then built to include the four stratification factors per protocol. Toxicity and quality-of-life measures were summarised descriptively. We did all statistical analyses in R (version 4.0.5). The study is registered with ClinicalTrials.gov, NCT03808662.

Role of the funding source

The funder of the study provided clinical and research support but had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From Jan 1, 2019, to July 31, 2021, 107 patients were screened and provided informed consent from seven treatment centres, of whom one withdrew consent. Of 106 patients, 51 were randomly assigned to the standard-of-care group and 55 to the SBRT group (figure 1). Four patients with NSCLC (two in each group) withdrew from the study before completing the required follow-up visits. One patient with breast cancer in the standard-of-care group also withdrew from the study before completing the follow-up visits to receive

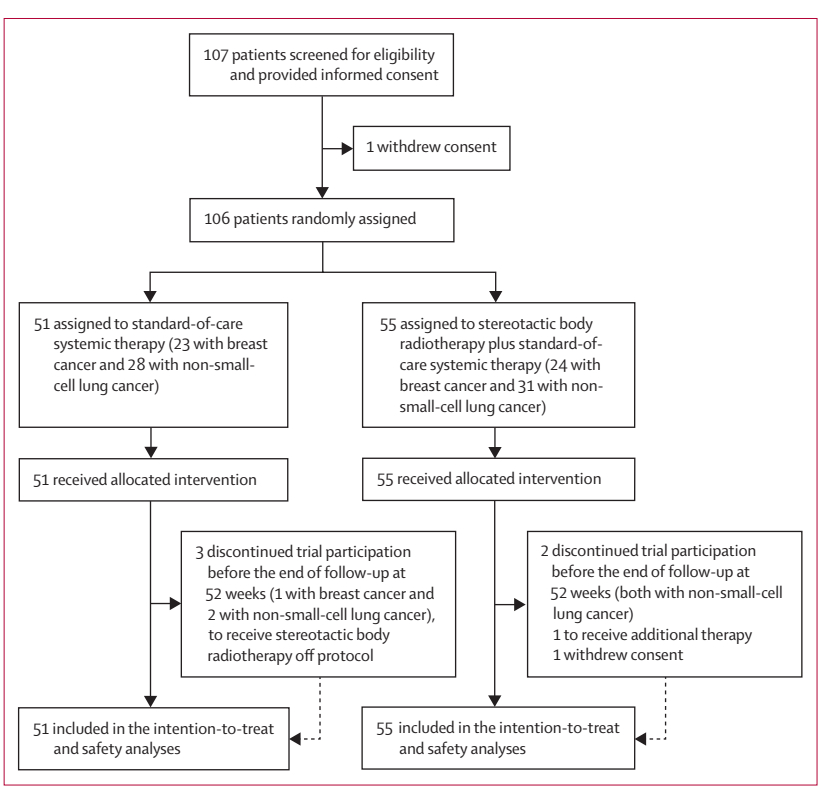

Figure 1: **Trial profile**

radiotherapy off protocol. These patients were included in the intention-to-treat analysis and were categorised as having stable disease at the time of study withdrawal.

47 (80%) of 59 patients with NSCLC had previously received immunotherapy (23 [82%] of 28 in the standard-of-care group and 24 [77%] of 31 in the SBRT group), whereas only ten (21%) of 47 patients with breast cancer had received immunotherapy (four [17%] of 23 in the standard-of-care group and six [25%] of 24 in the SBRT group; table 1). The interval between metastatic diagnosis and enrolment in the study was longer for patients with oligoprogressive breast cancer than for those with oligoprogressive NSCLC (29 months *vs* 18 months; p=0·0009). Most patients presented with more than one oligoprogressive lesion, and nearly half of the patients had more than five sites of metastatic disease, including both progressive and stable lesions (table 1). 16 (34%) patients with breast cancer had triple-negative disease. 51 (86%) patients with NSCLC did not have an actionable driver alteration. 12 (26%) of 47 patients with breast cancer and nine (15%) of 59 patients with NSCLC had documented brain metastases at baseline. 111 targets (ie, oligoprogressive lesions) were treated in patients in the SBRT group, with the most common radiotherapy doses administered being 27–30 Gy in three fractions (to 58 [52%] lesions) and 30–50 Gy in five fractions (to 21 [19%] lesions). The radiotherapy targets were non-spine bone metastases (34 [31%]), lung nodules (29 [26%]), lymph nodes (17 [15%]), spine (16 [14%]), liver (six [5%]), breast (five [5%]), and adrenal gland (four [4%]). 13 (25%) patients in the standard-of-care group and eight (15%) patients in the SBRT group had changed their systemic therapy at the time of enrolment. Additional patient characteristics including baseline performance status, initial staging modality, PD-L1 status, number of lines of systemic therapy received, and receipt of previous palliative radiotherapy are outlined in the appendix (p 14). All patients with breast cancer underwent identical imaging tests from baseline to subsequent follow-up visits. Only three (10%) of 31 patients with NSCLC in the SBRT group underwent different imaging tests between baseline and follow-up visits: one had a baseline CT and a follow-up PET-CT, whereas two had a baseline PET-CT and a follow-up CT.

The median follow-up was 11·6 months for patients in the standard-of-care group and 12·1 months for patients in the SBRT group. Follow-up for progression-free survival was stopped at 12 months after randomisation

	Overall		Breast cancer		Non-small-cell lung cancer	
	SOC (n=51)	SBRT (n=55)	SOC (n=23)	SBRT (n=24)	SOC (n=28)	SBRT (n=31)
Median age, years	67 (56–72)	70 (58–76)	56 (52–67)	65 (55–74)	70 (65–74)	71 (62–76)
Sex						
Female	35 (69%)	43 (78%)	23 (100%)	24 (100%)	12 (43%)	19 (61%)
Male	16 (31%)	12 (22%)	0	0	16 (57%)	12 (39%)
Received immunotherapy						
Yes	27 (53%)	30 (55%)	4 (17%)	6 (25%)	23 (82%)	24 (77%)
No	24 (47%)	25 (45%)	19 (83%)	18 (75%)	5 (18%)	7 (23%)
Number of oligoprogressive lesions						
1	13 (25%)	13 (24%)	5 (22%)	4 (17%)	8 (29%)	9 (29%)
2–5	38 (75%)	42 (76%)	18 (78%)	20 (83%)	20 (71%)	22 (71%)
Marker status						
Driver mutation	3 (6%)	5 (9%)	NA	NA	3 (11%)	5 (16%)
No driver mutation	25 (49%)	26 (47%)	NA	NA	25 (89%)	26 (84%)
Triple-negative breast cancer	9 (18%)	7 (13%)	9 (39%)	7 (29%)	NA	NA
Non-triple-negative breast cancer	14 (27%)	17 (31%)	14 (61%)	17 (71%)	NA	NA
Total number of metastatic sites						
1	5 (10%)	5 (9%)	1 (4%)	3 (13%)	4 (14%)	2 (6%)
2–5	22 (43%)	27 (49%)	7 (30%)	10 (42%)	15 (54%)	17 (55%)
>5	24 (47%)	23 (42%)	15 (65%)	11 (46%)	9 (32%)	12 (39%)
Had brain metastases						
Yes	12 (24%)	9 (16%)	7 (30%)	5 (21%)	5 (18%)	4 (13%)
No	39 (76%)	46 (84%)	16 (70%)	19 (79%)	23 (82%)	27 (87%)
Number of lines of systemic therapies received	2 (1–4)	2 (1–4)	4 (2–5)	3 (2–4)	1 (1–2)	2 (1–2)
Synchronous metastasis at initial cancer diagnosis	17 (33%)	22 (40%)	3 (13%)	5 (21%)	14 (50%)	17 (55%)

Data are median (IQR) or n (%). Percentages might not add up to 100% due to rounding. NA=not applicable. SBRT=stereotactic body radiotherapy. SOC=standard of care.

Table 1: **Baseline characteristics**

for all patients who did not progress further before then, defining the end of the study window. The median progression-free survival was 3·2 months (95% CI 2·0–4·5) for patients in the standard-of-care group versus 7·2 months (4·5–10·0) for patients in the SBRT group (hazard ratio [HR] 0·53, 95% CI 0·35–0·81; p=0·0035; figure 2A). Prespecified subgroup analysis of progression-free survival by disease site identified that the benefit of SBRT was driven by patients with NSCLC, who derived a significant improvement from SBRT, with the median progression-free survival increasing from 2·2 months (95% CI 2·0–4·5) for patients with NSCLC in the standard-of-care group to 10·0 months (7·2–not reached) for patients with NSCLC in the SBRT group (HR 0·41, 95% CI 0·22–0·75; p=0·0039; figure 2B). By contrast, SBRT did not significantly improve progression-free survival for patients with breast cancer (median progression-free survival 4·2 months [95% CI 1·8–5·5] in the standard-of-care group *vs* 4·4 months [2·5–8·7] in the SBRT group; HR 0·78, 95% CI 0·43–1·43; p=0·43; figure 2C). An exploratory analysis of the breast cancer cohort stratified by oestrogen receptor status yielded similar results (data not shown). In a multivariable Cox model adjusting for the four stratification factors and change of systemic therapy at enrolment, the progression-free survival benefit of SBRT remained substantial for patients with NSCLC (HR 0·33, 95% CI 0·16–0·66; p=0·0019) but not for patients with breast cancer (0·79, 0·37–1·65; p=0·53). SBRT was not associated with increased overall survival in the entire cohort (HR 0·99, 95% CI 0·55–1·81; p=0·40; appendix p 5) or disease-specific subgroups (appendix pp 6–7). Patients in the SBRT group remained on the current systemic therapy (median 8·1 months, 95% CI 5·1–15·0) for longer than those in the standard-of-care group (5·3 months, 3·0–7·6; p=0·014; appendix p 8). The time to initiation of a new therapy was longer among patients with NSCLC (11·0 months, 95% CI 5·8–not reached) than among those with breast cancer (3·9 months, 2·6–6·3; p=0·0030; appendix p 9). None of the 111 irradiated lesions among the 55 patients in the SBRT group progressed. 26 (59%) of 44 patients in the standard-of-care group with disease progression received salvage SBRT to progressive lesions, and 15 (36%) of 42 patients in the SBRT group with disease progression in either previously unstable or unirradiated sites or new lesions received further SBRT to these lesions.

Local therapy in patients with oligoprogressive cancer might alter patterns of anatomical progression (figure 3A). 29 (62%) patients with breast cancer who had disease progression after random assignment developed new lesions outside of the radiation field, regardless of treatment group assignment (figure 3B). A difference was observed in the anatomical pattern of disease progression in patients who did not receive SBRT; 14 (61%) of 23 patients with breast cancer developed new lesions compared with only four (14%) of

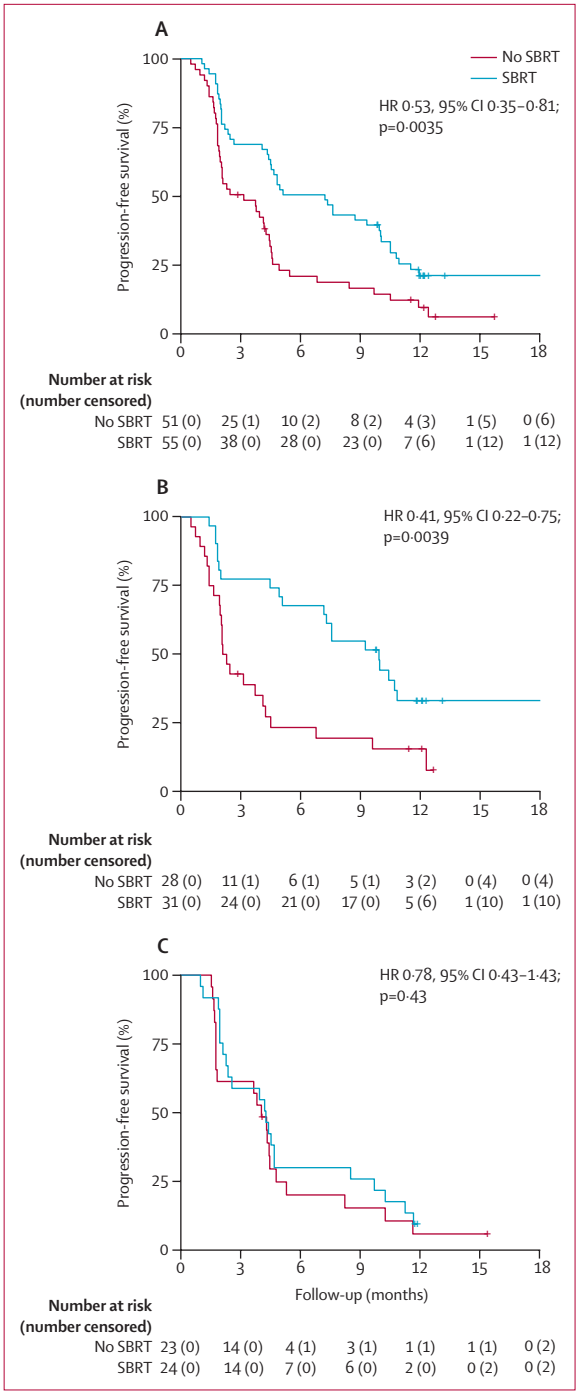

Figure 2: **Progression-free survival**
Progression-free survival in the entire cohort (A), patients with non-small-cell lung cancer (B), and patients with breast cancer (C). Tick marks indicate censored data. HR=hazard ratio. SBRT=stereotactic body radiotherapy.

28 patients with NSCLC (absolute difference 47%, 95% CI 19–74). Patients with NSCLC in the SBRT group had fewer progressions in pre-existing lesions than those with NSCLC in the standard-of-care group (eight [26%] of 31 patients *vs* 19 [68%] of 28 patients; figure 3B). This

observation was consistent with systemic blood-borne markers of tumour burden as evidenced by the evaluation of cell-free DNA dynamics during therapy (figure 3C). 58 (55%) patients (26 with breast cancer and 32 with NSCLC) had paired blood samples collected at baseline and at the 8-week timepoint. In an exploratory analysis of these samples, we evaluated the changes in the mutant allele fraction and cell-free DNA content from baseline to first follow-up. Both mutant allele fraction and ctDNA fraction were significantly correlated with disease burden (figure 3C; appendix p 11). In the NSCLC cohort, patients who received SBRT plus standard of care had a significant decrease in median allele fraction between baseline and follow-up

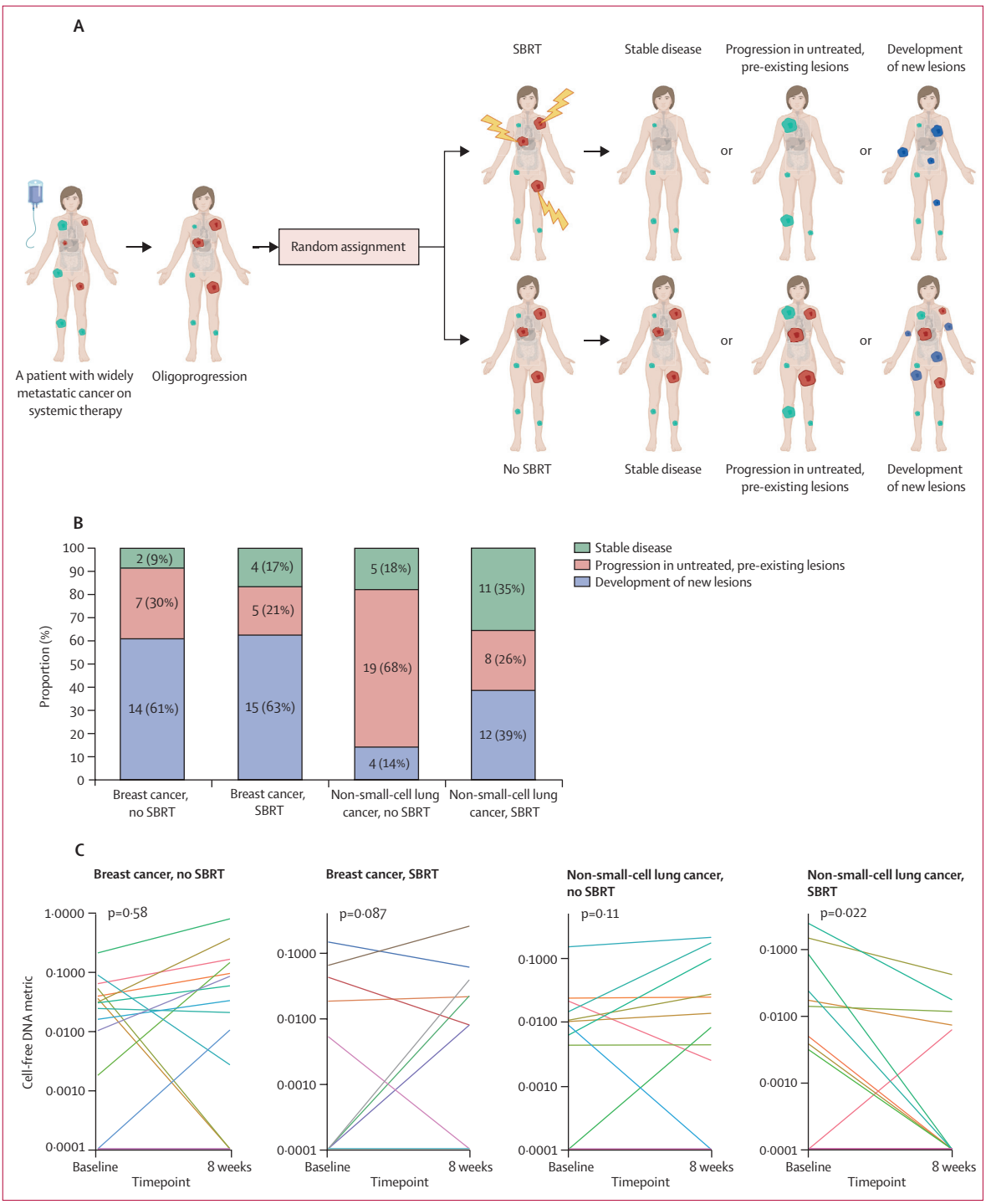

Figure 3: **Patterns of disease progression**
(A) Visual illustration indicating distinct patterns of disease progression after treatment. Figure created with BioRender.com. (B) Patterns of disease progression by disease site and treatment group. (C) Assessment of systemic disease burden with circulating tumour DNA analysis before and 8 weeks after enrolment. Each line represents one patient. SBRT=stereotactic body radiotherapy.

	SOC group (n=51)	SBRT group (n=55)
Any grade ≥2	21 (41%)	34 (62%)
Haematological		
Anaemia		
Grade 2	6 (12%)	13 (24%)
Grade 3	0	3 (5%)
INR increased		
Grade 2	1 (2%)	0
Grade 3	0	2 (4%)
Lymphocyte count decreased		
Grade 2	8 (16%)	8 (15%)
Grade 3	1 (2%)	12 (22%)
Grade 4	1 (2%)	2 (4%)
Neutrophil count decreased		
Grade 2	5 (10%)	6 (11%)
Grade 3	0	6 (11%)
Grade 4	1 (2%)	0
Platelet count decreased		
Grade 2	0	2 (4%)
Grade 3	0	2 (4%)
White blood cell count decreased		
Grade 2	4 (8%)	7 (13%)
Grade 3	0	5 (9%)
Gastrointestinal		
Alanine aminotransferase increased		
Grade 2	0	1 (2%)
Alkaline phosphatase increased		
Grade 2	1 (2%)	0
Aspartate aminotransferase increased		
Grade 2	1 (2%)	0
Grade 3	0	1 (2%)
Blood bilirubin increased		
Grade 2	1 (2%)	2 (4%)
Diarrhoea		
Grade 2	0	1 (2%)
Gastro-oesophageal reflux disease		
Grade 2	0	3 (5%)
Hypoalbuminaemia		
Grade 2	2 (4%)	4 (7%)
Nausea		
Grade 2	0	1 (2%)
Renal		
Creatinine increased		
Grade 2	0	4 (7%)
Electrolytes		
Hypercalcaemia		
Grade 2	2 (4%)	0
Hyperglycaemia		
Grade 2	3 (6%)	2 (4%)
Grade 3	1 (2%)	4 (7%)
Grade 4	0	1 (2%)
Hypocalcaemia		
Grade 2	1 (2%)	2 (4%)
Grade 4	1 (2%)	0
Hypokalaemia		
Grade 3	1 (2%)	0
Hyponatraemia		
Grade 3	0	1 (2%)
Hypophosphataemia		
Grade 3	0	2 (4%)
Pulmonary		
Dyspnoea		
Grade 3	1 (2%)	0
Hypoxia		
Grade 3	1 (2%)	0
Other		
Pneumonitis		
Grade 3	0	1 (2%)
Brachial plexopathy		
Grade 2	0	1 (2%)
Pain exacerbation		
Grade 2	1 (2%)	1 (2%)
Grade 3	0	1 (2%)
Sinusitis		
Grade 2	0	1 (2%)

INR=international normalised ratio. SBRT=stereotactic body radiotherapy. SOC=standard of care.

Table 2: **Summary of adverse events**

(p=0·022), whereas those who only received standard-of-care systemic therapy had no significant change in median allele fraction between baseline and follow-up (p=0·11). By contrast, for patients with breast cancer, no significant difference in allele fraction from baseline to follow-up between treatment groups was observed (figure 3C), or after stratifying by oestrogen receptor status (appendix p 10). Similar observations were made when the ctDNA fraction rather than the mutant allele fraction was used to define the changes in ctDNA (appendix p 12).

Any grade 2 or worse adverse events occurred in 21 (41%) patients in the standard-of-care group and 34 (62%) patients in the SBRT group (table 2). The most common toxicities of grade 2 or worse in both groups were decreased lymphocyte count (22 [40%] patients in the SBRT group *vs* ten [20%] patients in the standard-of-care group), anaemia (16 [29%] patients *vs* six [12%] patients), and decreased neutrophil count (12 [22%] patients *vs* six [12%] patients). Treatment-related grade 2 or worse toxicities occurred in nine (16%) patients in the SBRT group, including grade 2 gastro-oesophageal reflux disease in three patients, grades 2 and 3 pain exacerbation in two patients, grade 3 radiation pneumonitis in one patient, grade 2 brachial plexopathy in one patient, and grade 2 anaemia in two patients. The descriptive

summary of quality-of-life scores is presented in the appendix (p 13). The quality-of-life scores were similar between patients in the standard-of-care and SBRT groups. However, for patients in the standard-of-care group, a decline in quality-of-life scores was observed at week 36, specifically in global health status, physical functioning, and social functioning. These declines were influenced by an extremely small sample size (one patient in the standard-of-care group and three patients in the SBRT group) at that specific timepoint, mainly due to very few patients who remained progression-free. As a result, no statistical comparison was done to assess the significance of this decline.

Discussion

Previous evidence has supported metastasis-directed local therapy in patients with oligometastatic disease;[5–9] however, randomised clinical trials interrogating the role of local ablative therapy for patients with oligoprogressive metastatic cancer have not been reported. Previous studies examining local therapy for oligoprogressive cancers have been primarily single-arm retrospective literature reviews of heterogeneous patient populations, with different metastatic disease burdens, treated with varying systemic therapy, and without adequate comparison groups to allow rigorous assessment of the potential benefits of local ablative therapy in this population.[17,23–25]

In accordance with the study protocol, the interim analysis in this study was planned to assess the response of the entire cohort using a stratified log-rank test, taking into account four predetermined stratification factors. The median progression-free survival was more than twice longer for patients receiving SBRT plus standard of care than for those receiving standard of care alone (7·2 months *vs* 3·2 months), and for patients with NSCLC in a subgroup analysis, it was more than four times longer if they were treated with SBRT plus standard of care compared with standard of care only (10·0 months *vs* 2·2 months). However, no progression-free survival benefit was observed in patients with oligoprogressive breast cancer, regardless of oestrogen receptor status. The pattern of disease progression after randomisation was also notably different between the two cohorts. Patients with breast cancer were more likely to develop new metastatic lesions, whereas most patients with NSCLC primarily progressed from pre-existing, non-irradiated lesions. Analyses of paired pre-randomisation and post-randomisation blood samples showed that SBRT led to changes in ctDNA metrics in patients with NSCLC, but not in patients with breast cancer. Measurements of systemic disease burden by mutant allele fraction and ctDNA fraction were concordant with observed clinical patterns of disease progression, with SBRT only resulting in a decrease in mutant allele fraction and ctDNA in patients with NSCLC.

The observed clinical outcomes and genomic alterations provide compelling evidence of the identification of oligoprogression in patients with metastatic NSCLC, who could therefore benefit from local ablative therapy. This finding differed from the systemic progression observed in patients with breast cancer, highlighting the limitations of the current radiographic definition of oligoprogression when selecting patients with metastatic breast cancer for local therapy. The results from this study might also indicate that there is no discernible oligoprogression in metastatic breast cancer, presenting a challenge in identifying and effectively treating these patients with local therapy. However, the sensitivity of the ctDNA detection assay, variations in ctDNA release between metastatic breast cancer and NSCLC, and fluctuations in ctDNA dynamics might have contributed to the observed outcomes.

The differences in clinical characteristics between patients with breast cancer and those with NSCLC in our study should be considered when interpreting the results of the study. Patients with breast cancer enrolled on average had more total sites of metastasis, a considerable proportion of triple-negative disease, and a higher number of previous systemic therapies, potentially reflecting more advanced disease, compared with patients with NSCLC. The interval between metastatic diagnosis and enrolment in the study was longer for patients with oligoprogressive breast cancer than for those with oligoprogressive NSCLC, potentially implying a more diverse tumour biology with increased heterogeneity and drug-induced resistance. Additionally, the findings of this trial might have limited generalisability because the majority of patients with NSCLC included in the study did not have any actionable driver mutation. However, results from this trial are in alignment with evidence from the oligometastatic cancer literature: several clinical trials have suggested enhanced survival rates in patients with oligometastatic NSCLC after ablative radiotherapy.[7,9] By contrast, the NRG-BR002 study reported that ablative radiotherapy did not confer a survival benefit in patients with oligometastatic breast cancer.[26]

This study was not powered to detect an overall survival benefit and was closed early due to a larger than anticipated progression-free survival benefit, probably leading to a further reduction in our ability to detect a possible long-term overall survival benefit. Any survival effect could have been compromised by the fact that 59% of patients in the standard-of-care group received off-protocol SBRT treatment after disease progression. A large phase 3 clinical trial will be required to show the presence or absence of an overall survival benefit, which we consider to be a crucial next step for future research. Nonetheless, prolonged progression-free survival—preserving disease control without requiring a shift to a new and potentially more toxic systemic therapy—is arguably a meaningful benefit for patients with metastatic disease, even in the absence of a definitive survival benefit.

Patients in the SBRT group were able to stay on the existing systemic therapy regimen for a longer period of time, with only modest increases in toxicities. These

findings challenge the current treatment paradigm for oligoprogressive metastatic NSCLC and highlight the potential value of local ablative therapies in this patient population. Quality-of-life scores were equivalent between the two groups. Evidence recommends that monitoring the deterioration of health-related quality of life in patients with metastatic cancer should be prioritised for any therapeutic intervention.[27] Additional studies of the clinical utility of SBRT including high-quality data instruments for quality-of-life assessment might help define a patient population that could benefit the most from this intervention.

Several ongoing randomised trials are currently investigating the potential benefits of ablative radiotherapy in patients with oligoprogressive cancer, all with progression-free survival as their primary endpoint. The STOP trial (NCT02756793) is a phase 2 randomised clinical trial involving 90 patients with oligoprogressive metastatic cancers. Initially designed to accrue only patients with NSCLC, the study later expanded its inclusion criteria to include patients with any type of cancer. The trial has completed accrual, and results are expected to be reported soon. Additionally, two ongoing randomised trials are specifically investigating the potential benefit of SBRT in patients with oligoprogressive NSCLC, the HALT trial (NCT03256981) and the SUPPRESS-NSCLC trial (NCT04405401), with results from these studies expected to provide further insights into the efficacy of SBRT.

Our study has some limitations. Despite our focus on patients with oligoprogressive breast cancer and NSCLC, there is inherent heterogeneity within each histology, such as driver gene alteration status, overall disease burden, metastatic disease interval, and previous number of lines of systemic therapy. The small number of patients receiving non-immunotherapy-based treatment in the NSCLC group restricted a more in-depth analysis of the combined impact of immunotherapy and radiotherapy. Additionally, the decision to switch systemic therapy was left to the discretion of the treating physician, which resulted in variable systemic therapy decisions after randomisation. However, this variability in treatment decisions mirrored real-world clinical practice. Despite the variability in treatment decisions, the observed progression-free survival benefit persisted after controlling for changes in systemic therapy at enrolment in the NSCLC cohort, while remaining null in the breast cancer cohort. The unblinded and open-label design of the trial could have introduced a degree of bias in patient-reported outcomes, which must be carefully considered when interpreting the results. Due to the COVID-19 pandemic occurring a year into the study, only 55% of patients had paired blood samples available for ctDNA analysis, limiting further in-depth analysis of ctDNA metrics. Lastly, the selection of eligible patients involved the use of different baseline staging methods, potentially resulting in varying sensitivities in disease detection. To mitigate this potential discrepancy, we made efforts to standardise the staging imaging methods for each patient from baseline to subsequent follow-up visits. As a result of these efforts, we achieved a high level of consistency, with only three patients undergoing different staging examinations between baseline and follow-up visits. These limitations highlight the importance of rigorous study design and the need for careful consideration of external factors that could affect the reliability and validity of trial findings.

Despite these limitations, the results from this prospective randomised clinical trial support the existence of oligoprogression in patients with metastatic NSCLC amenable to local therapy. By contrast, no benefit of SBRT was observed in patients with breast cancer. The clinical findings were further verified by the cell-free DNA analysis, which underscores a potential use for ctDNA assessment after SBRT in patient with oligoprogressive cancer. To validate the efficacy of SBRT in patients with oligoprogressive NSCLC, further research in a well defined patient population is required through a phase 3 trial.

Contributors

CJT, JTY, and SNP conceptualised and developed the study. NS, AFS, JE, DG, RY, DYG, AN, IP, SM, AS, TT, PD, AR, EFG, DRG, NYL, MER, and CMR provided feedback to the study design, patient accrual, and data presentation. JP, MB, JSR-F, and NR led the analysis and interpretation of ctDNA data. JF and ZZ did the clinical data analysis and interpretation. CJT wrote the first draft of the report with input from NR and SNP. All authors contributed to the final version of the report. CJT, JF, and ZZ had directly accessed and verified the underlying data reported in the manuscript. CJT had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

CJT is on the advisory board of Nanobiotix and Varian Medical, and received consultation fees and honorarium support from Varian Medical. AR received grants from Varian Medical, AstraZeneca, Merck, Boehringer Ingelheim, Pfizer, and the National Cancer Institute at the National Institutes of Health. DRG is a researcher with AstraZeneca, Bristol Myers Squibb, and Merck; is on the advisory board of Grail, Olympus, Johnson & Johnson, Varian Medical, and Medtronic; and served as a speaker for MedLearning Group. NYL is on the advisory board of Merck, Merck EMD, Nanobiotix, and Galera Therapeutics; and received consulting fees from Shanghai JoAnn Medical Technology, Yingming Consulting, and Varian Medical. NR received research support from Invitae. All other authors declare no competing interests.

Data sharing

De-identified individual participant data that underly the results reported in this Article will be made available beginning 12 months and ending 36 months after publication. Data will be made available to investigators who intend to carry out an individual participant data meta-analysis and whose proposed use of the data has been approved by an independent review committee. Proposals should be directed to powells@mskcc.org; to gain access, data requestors will need to sign a data access agreement.

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