Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial

David A Palma, Robert Olson, Stephen Harrow, Stewart Gaede, Alexander V Louie, Cornelis Haasbeek, Liam Mulroy, Michael Lock, George B Rodrigues, Brian P Yaremko, Devin Schellenberg, Belal Ahmad, Gwendolyn Griffioen, Sashendra Senthi, Anand Swaminath, Neil Kopek, Mitchell Liu, Karen Moore, Suzanne Currie, Glenn S Bauman, Andrew Warner, Suresh Senan

Summary

Background The oligometastatic paradigm suggests that some patients with a limited number of metastases might be cured if all lesions are eradicated. Evidence from randomised controlled trials to support this paradigm is scarce. We aimed to assess the effect of stereotactic ablative radiotherapy (SABR) on survival, oncological outcomes, toxicity, and quality of life in patients with a controlled primary tumour and one to five oligometastatic lesions.

Methods This randomised, open-label phase 2 study was done at 10 hospitals in Canada, the Netherlands, Scotland, and Australia. Patients aged 18 or older with a controlled primary tumour and one to five metastatic lesions, Eastern Cooperative Oncology Group score of 0–1, and a life expectancy of at least 6 months were eligible. After stratifying by the number of metastases (1–3 *vs* 4–5), we randomly assigned patients (1:2) to receive either palliative standard of care treatments alone (control group), or standard of care plus SABR to all metastatic lesions (SABR group), using a computer-generated randomisation list with permuted blocks of nine. Neither patients nor physicians were masked to treatment allocation. The primary endpoint was overall survival. We used a randomised phase 2 screening design with a two-sided α of 0·20 (wherein p<0·20 designates a positive trial). All analyses were intention to treat. This study is registered with ClinicalTrials.gov, number NCT01446744.

Findings 99 patients were randomised between Feb 10, 2012, and Aug 30, 2016. Of 99 patients, 33 (33%) were assigned to the control group and 66 (67%) to the SABR group. Two (3%) patients in the SABR group did not receive allocated treatment and withdrew from the trial; two (6%) patients in the control group also withdrew from the trial. Median follow-up was 25 months (IQR 19–54) in the control group versus 26 months (23–37) in the SABR group. Median overall survival was 28 months (95% CI 19–33) in the control group versus 41 months (26–not reached) in the SABR group (hazard ratio 0·57, 95% CI 0·30–1·10; p=0·090). Adverse events of grade 2 or worse occurred in three (9%) of 33 controls and 19 (29%) of 66 patients in the SABR group (p=0·026), an absolute increase of 20% (95% CI 5–34). Treatment-related deaths occurred in three (4·5%) of 66 patients after SABR, compared with none in the control group.

Interpretation SABR was associated with an improvement in overall survival, meeting the primary endpoint of this trial, but three (4·5%) of 66 patients in the SABR group had treatment-related death. Phase 3 trials are needed to conclusively show an overall survival benefit, and to determine the maximum number of metastatic lesions wherein SABR provides a benefit.

Funding Ontario Institute for Cancer Research and London Regional Cancer Program Catalyst Grant.

Lancet 2019; 393: 2051–58

Published Online
April 11, 2019
http://dx.doi.org/10.1016/S0140-6736(18)32487-5

See Comment page 2013

London Health Sciences Centre, London, ON, Canada (D A Palma MD, S Gaede PhD, A V Louie MD, M Lock MD, Prof G B Rodrigues MD, B P Yaremko MD, B Ahmad MD, Prof G S Bauman MD, A Warner MSc); **British Columbia Cancer, Centre for the North, Prince George, BC, Canada** (R Olson MD); **Beatson West of Scotland Cancer Centre, Glasgow, UK** (S Harrow PhD, K Moore MSc, S Currie MSc); **Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, Netherlands** (C Haasbeek MD, G Griffioen MD, Prof S Senan FRCR); **Nova Scotia Cancer Centre, Halifax, NS, Canada** (L Mulroy MD); **British Columbia Cancer, Surrey Centre, Surrey, BC, Canada** (D Schellenberg MD); **Alfred Health Radiation Oncology, Melbourne, VIC, Australia** (S Senthi MD); **Juravinski Cancer Centre, Hamilton, ON, Canada** (A Swaminath MD); **McGill University Health Centre, Montreal, QC, Canada** (N Kopek MD); **and British Columbia Cancer, Vancouver Centre, Vancouver, BC, Canada** (M Liu MD)

Correspondence to:
Dr David Palma, London Health Sciences Centre, London, ON N6A 5W9, Canada
david.palma@lhsc.on.ca

Introduction

Historically, the treatment of patients with metastatic solid tumours has been based on systemic therapies that aim to delay progression and extend life, but not to eradicate the disease completely.[1,2] The oligometastatic paradigm, formally defined in the 1990s[3] but anecdotally reported as early as the 1930s,[4] suggests that in some patients, metastatic disease is not widespread, but is constrained to develop in only a small number of sites because of anatomical and physiological factors.[3] This paradigm suggests that patients with oligometastases should be amenable to a curative treatment approach.[3]

Clinical evidence to support improved treatment outcomes in the oligometastatic state has generally been limited to non-randomised observational studies.[5] Many of these studies, but not all, suggest that the treatment of oligometastatic disease with ablative therapies can lead to better-than-expected survival, compared with a general population of patients with metastatic disease.[6,7] However, these promising results could be due to selection bias, with the inclusion of fit patients with low-burden, indolent cancers.[5,7] Nevertheless, the use of ablative therapies has increased in many jurisdictions worldwide, albeit with substantial geographical variability in practice.[8,9] Interest in treating oligometastatic disease is also increasing

Research in context

Evidence before this study

Several recent systematic reviews examined the effect of ablative therapies in patients with oligometastatic cancers. No previous randomised trials were identified in patients with oligometastases, in which the primary endpoint was a comparison of overall survival between an ablative treatment group (eg, stereotactic ablative radiotherapy [SABR] or surgery) and a group that did not receive ablative therapy. In patients with one to nine hepatic metastases from colorectal cancer, a secondary analysis of a randomised trial assessing systemic therapy with or without radio-frequency ablation showed an overall survival benefit with the use of radio-frequency ablation to all hepatic lesions. Three randomised trials using surrogate endpoints, such as progression-free survival, have shown benefits of ablative therapies in oligometastatic prostate and lung cancers. Findings are based on a search of PubMed from inception to Aug 1, 2018, using search terms related to "oligometastatic" (eg, "limited metastatic", "solitary metastasis", and "oligometastatic"), and common cancer types (eg, "breast cancer", "prostate cancer", and "lung cancer"), limited to English language randomised trials. A similar search for systematic reviews was undertaken and their reference lists were hand-searched.

Added value of this study

This study found that the use of SABR in patients with controlled primary tumours and one to five oligometastases achieved a 13-month improvement in overall survival, with a doubling of progression-free survival, at the cost of increased risk of toxicity, including a 4·5% risk of grade 5 toxicity. These findings represent the strongest level of evidence, thus far, in support of the existence of an oligometastatic state.

Implications of all the available evidence

Although further trials are needed, the emerging evidence supports the existence of an oligometastatic state, and that patients with a limited number of metastases might be amenable to curative-intent treatment strategies.

because of improvements in systemic therapy, as has been observed with molecular targeted therapies[10] and immune checkpoint inhibitors.[11]

Stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiation therapy, is a modern radiation technique that delivers high doses of radiation to small tumour targets with use of highly conformal techniques (appendix p 2).[12] SABR is non-invasive, delivered on an outpatient basis, and is used to target lesions in the lungs, brain, liver, adrenals, and bone, among other locations.

See Online for appendix

To our knowledge, the oligometastatic paradigm has not been directly tested before in a randomised trial; namely, no trial has evaluated whether eradicating oligometastases that have propagated through the systemic circulatory system improves overall survival. In this randomised controlled trial, we aimed to assess standard of care palliative treatments with or without SABR in patients with a controlled primary tumour and up to five metastatic lesions.

Methods

Study design and participants

The Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastases (SABR-COMET) trial was an investigator-initiated, multicentre, international, open-label, parallel-group, phase 2 randomised study. Patients were enrolled at ten hospital centres located in Canada, the Netherlands, the UK, and Australia.

Patients were required to be aged 18 years or older, with good performance status (Eastern Cooperative Oncology Group score 0–1), and a life expectancy of at least 6 months, as judged by the enrolling physician. Their primary tumour must have been treated definitively at least 3 months before enrolment, with no progression at that site since the definitive treatment as established by imaging. Patients were required to be discussed at a multidisciplinary tumour board or quality-assurance rounds before randomisation, with consensus opinion that entry into the study was appropriate. Biopsy of a metastasis was not required but was preferred. All metastatic lesions had to be amenable to SABR, and a maximum of three metastases in any one organ was allowed with no more than five metastases in total.

Pre-enrolment imaging requirements included: (1) imaging of the brain, for tumours with a propensity for brain metastasis, with CT or MRI; (2) body imaging with either a PET-CT or CT of the neck, chest, abdomen, and pelvis plus bone scan; and (3) MRI of the spine for patients with vertebral metastases.

The main exclusion criteria included serious medical comorbidities precluding radiotherapy, bone metastasis in a femoral bone, the presence of one to three brain metastases with no disease elsewhere (as randomisation to the control group would not be recommended), previous radiotherapy to a site requiring treatment, malignant pleural effusion, tumour within 3 mm of spinal cord on MRI, dominant brain metastasis requiring surgical decompression, pregnancy, or lactation. Appropriate regulatory approval, including ethical approval, was obtained in all jurisdictions. All patients provided written informed consent. An abridged protocol has been previously published,[13] and the full protocol is available in the appendix.

Randomisation and masking

Patients with a controlled primary tumour and one to five metastatic lesions were randomly assigned in a 1:2 ratio to either standard of care palliative treatments (control group) or standard of care plus SABR to all sites

of metastatic disease (SABR group). Patients were assigned to groups using a computer-generated randomisation list with permuted blocks of nine, stratified by the number of metastases (1–3 *vs* 4–5). Patients were allocated after receipt of a completed enrolment form and other regulatory documents (including consent). These documents were received by fax at the coordinating centre and the treatment allocation was communicated by email. On receipt of these documents, enrolment and assignment were done by an arms-length trial coordinator not involved in clinical management. Neither patients nor enrolling physicians were masked to treatment allocation.

Procedures

In the control group, radiotherapy was delivered according to the standard principles of palliative radiation, with the goal of alleviating symptoms or preventing anticipated complications of progression. Patients in the control group were not to receive SABR or radical radiation doses. Recommended treatment fractionations depended on the tumour location and indication, and ranged from 8 Gy in one fraction to 30 Gy in ten fractions.

In the SABR group, patients received stereotactic radiation to all sites of metastatic disease, with the goal of achieving disease control while minimising potential toxicities. A full table of allowable SABR doses is provided in the protocol (appendix). In general, allowable doses ranged from 30–60 Gy in three to eight fractions, depending on target size and location. Single fractions of 16–24 Gy were permitted for targets in the brain and vertebrae. In all situations, the protocol recommended that normal tissue tolerance doses not be exceeded, even if the dose to all or part of the target had to be reduced. Quality assurance included mock treatment plans completed for each centre joining the study, and a requirement for institutional peer review of all SABR plans.

In both groups, standard of care systemic therapy was recommended as indicated, using a pragmatic approach wherein the choice of systemic agents was at the discretion of the medical oncologist. It was not possible to prespecify the standard of care systemic therapy in this trial because of the various types of primary cancer eligible, and the anticipated changes in standard of care for some types of primary cancer during the timeframe of the trial. In the SABR group, concurrent chemotherapy or targeted therapy was not permitted within the 4 weeks before SABR. These therapies were stopped for a 4-week window, SABR was delivered, and then systemic therapy could be resumed.

Patients were seen every 3 months after randomisation for the first 2 years, and every 6 months thereafter, with regular imaging as outlined in the appendix. The protocol was later amended to continue annual visits until year 10. After disease progression, ongoing scans were done at the discretion of treating physicians. Patients in the SABR group who developed new metastatic deposits were eligible for further SABR at those sites as salvage. Any further palliative systemic therapy and palliative radiation therapy after progression were at the discretion of the treating physicians.

Outcomes

The primary endpoint was overall survival, defined as time from randomisation to death from any cause. Prespecified secondary endpoints were: quality of life (QOL), assessed with the Functional Assessment of Cancer Therapy: General (FACT-G); toxicity, assessed by the National Cancer Institute Common Toxicity Criteria version 4; progression-free survival, defined as time from randomisation to disease progression at any site or death; proportion of patients with lesional control; and number of cycles of further chemotherapy or systemic therapy.

Statistical analysis

We used a randomised phase 2 screening design,[14] with a two-sided α of 0·20 and a power of 80% as recommended for such studies.[14] In a phase 2 screening design, the α level is set higher than the 0·05 level that is used for a phase 3 design, recognising that even if the phase 2 trial is positive (ie, if the ultimate p value is less than 0·20), such a positive result is not usually considered definitive without a subsequent phase 3 trial. The choice of a two-sided α of 0·20, rather than the usual one-sided testing for phase 2 randomised trials[15] allowed for the possibility of finding inferior overall survival with SABR due to toxicity. We estimated that the median survival of the control group after randomisation would be 9 months. To detect a 6-month improvement in median survival, and assuming 5% of patients are lost to follow-up, 99 patients were required (33 in the control group and 66 in the SABR group).

All analyses were based on the intention-to-treat principle. Overall survival and progression-free survival were

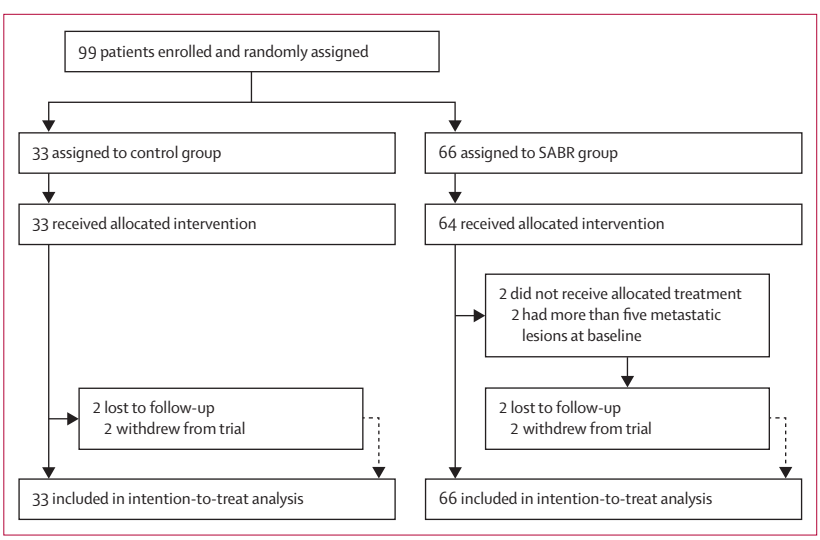

Figure 1: **Trial profile**
SABR=stereotactic ablative radiotherapy.

	Control group (n=33)	SABR group (n=66)
Age	69 (64–75)	67 (59–74)
Sex		
Men	19 (58%)	40 (61%)
Women	14 (42%)	26 (39%)
Site of original primary tumour		
Breast	5 (15%)	13 (20%)
Colorectal	9 (27%)	9 (14%)
Lung	6 (18%)	12 (18%)
Prostate	2 (6 %)	14 (21%)
Other	11 (33%)	18 (27%)
Time from diagnosis of primary tumour to randomisation (years)	2·3 (1·3–4·5)	2·4 (1·6–5·3)
Number of metastases		
1	12 (36 %)	30 (46%)
2	13 (40%)	19 (29%)
3	6 (18%)	12 (18%)
4	2 (6%)	2 (3%)
5	0 (0%)	3 (5%)
Location of metastases		
Adrenal	2/64 (3%)	7/127 (6%)
Bone	20/64 (31%)	45/127 (35%)
Liver	3/64 (5%)	16/127 (13%)
Lung	34/64 (53%)	55/127 (43%)
Other*	5/64 (8%)	4/127 (3%)

Data are n (%), n/N (%), or median (IQR). SABR=stereotactic ablative radiotherapy. *Other comprises brain (n=3 lesions in control group; n=1 lesion in SABR group), lymph nodes (n=1 lesion in control group; n=3 lesions in SABR group), and para-renal (n=1 lesion in control group).

Table 1: **Baseline characteristics**

calculated using the Kaplan-Meier method with differences compared with the stratified log-rank test. Hazard ratios (HRs) were calculated using Cox regression adjusted for stratification. QOL at 6 months was measured using FACT-G scores, with differences between groups tested with the two-sample *t* test. Differences in rates of grade 2 or higher toxicity and lesional control rate between groups were tested using the χ^2 test or Fisher's exact test as appropriate.

The prespecified endpoint of number of cycles of further chemotherapy or systemic therapy was not reliably ascertainable because many patients received systemic therapy at other centres during the follow-up period and the precise number of cycles was not always clear. We therefore report further systemic therapy as a binary variable (ie, further systemic therapy received: yes *vs* no) with differences compared using the Fisher's exact test, which should be considered a post-hoc analysis. All statistical analyses were done using SAS version 9.4 software.

An interim analysis was undertaken in June, 2015, after 50 patients were accrued to establish whether the trial was to continue to full accrual or stop early, as determined by the data safety monitoring committee. The trial could have been stopped if the prespecified Haybittle–Peto boundary (a difference in overall survival meeting a threshold of p<0·001, with no p value penalty in the final analysis) was met at the interim analysis, or if excessive rates of grade 3–5 adverse events were observed in the SABR group by the data safety monitoring committee at any time. Neither of these conditions was met; therefore the trial continued to full accrual. The protocol anticipated 4 years of accrual and 1 year of further follow-up. The trial closed in August, 2016, and after 1 year of follow-up and time to resolve data queries, the dataset was locked for outcomes on Jan 18, 2018. This study is registered with ClinicalTrials.gov, number NCT01446744.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Feb 10, 2012, and Aug 30, 2016, 99 patients were enrolled at ten centres; 33 were randomly assigned to the control group and 66 to the SABR group (figure 1). It was not possible to capture the number of patients assessed for eligibility, because referring physicians were able to discuss cases with participating investigators on an ad-hoc basis without formal referral, and such discussions were not tracked. Baseline characteristics are shown in table 1. The SABR group had a preponderance of patients with prostate cancer and had all the patients with five metastases. Violations of eligibility criteria or protocol treatments are detailed in the appendix. 16 (48%) of 33 patients in the control group and 30 (45%) of 66 patients in the SABR group underwent PET-CT before enrolment.

In the SABR group, the most common radiation dose fractionations used were 35 Gy in five fractions (for 39 targets), 60 Gy in eight fractions (19 targets), and 54 Gy in three fractions (16 targets). Eight (12%) of 66 patients in this group also received salvage SABR to new metastatic sites upon disease progression, and two received other ablative therapies after disease progression: one had a new liver metastasis treated with microwave ablation, and another underwent surgical resection for both a new metastasis (hip) and one that progressed after SABR (rib).

The median follow-up was 25 months (IQR 19–54) in the control group versus 26 months (23–37) in the SABR group. The primary outcome event, death from any cause, occurred in 16 (48%) of 33 patients in the control group and 24 (36%) of 66 patients in the SABR group. Median overall survival was 28 months (95% CI 19–33) in the control group *vs* 41 months (26–not reached) in the SABR group (HR 0·57, 95% CI 0·30–1·10; stratified log-rank p=0·090; figure 2A).

Progression events occurred in 67 patients: 39 (59%) of 66 patients in the SABR group and 28 (85%) of 33 patients in the control group. Of the 39 patients in the SABR group with progression of disease, 31 (79%) developed new metastases only, one (3%) had progression of treated lesions only, and seven (18%) had both. Similarly, of the 28 patients in the control group, 13 (46%) developed new metastases only, eight (29%) had enlargement of lesions only, and seven (25%) patients had both. Median progression-free survival was 6·0 months (95% CI 3·4–7·1) in the control group *vs* 12 months (6·9–30·4) in the SABR group (HR 0·47, 95% CI 0·30–0·76; stratified log-rank p=0·0012; figure 2B)

The proportion of patients with lesional control (ie, the absence of progression in the lesions initially present at randomisation) was 49% (28 of 57 assessable lesions) in the control group and 75% (75 of 100 assessable lesions) in the SABR group (p=0·0010), represented by an absolute increase of 26% (95% CI 10–41). For the 100 assessable lesions treated in the SABR group, 44 (44%) remained stable, 15 (15%) showed a partial response, and 16 (16%) showed a complete response

There were no significant differences in overall mean FACT-G scores at 6 months (82·5 [SD 16·4] in the control group *vs* 82·6 [16·6] in the SABR group; p=0·99), or in any of the physical, social, functional, or emotional QOL subscales (all p>0·40; appendix).

Adverse events are shown in table 2. Adverse events of grade 2 or more related to treatment occurred in three (9%) of 33 patients in the control group and 19 (29%) of 66 patients in the SABR group (p=0·026), an absolute increase of 20% (95% CI 5–34). The most common treatment-related toxic effects of grade 2 or worse in the SABR group were fatigue (n=4), dyspnoea (n=2), and pain (including muscle, bone, and other, total n=8). There were three treatment-related grade 5 events in the SABR group (4·5%, 95% CI 0–10), due to deaths from radiation pneumonitis (n=1), pulmonary abscess (n=1), and subdural haemorrhage after surgery to repair a SABR-related perforated gastric ulcer (n=1); see appendix for further details of treatment-related grade 5 events. After randomisation, 53 (54%) of 99 patients received palliative systemic therapy, and 34 (34%) of 99 patients received palliative, standard of care (non-SABR) radiotherapy. The two groups did not differ in the receipt of systemic therapy (19 [58%] of 33 patients in the control group *vs* 34 [52%] of 66 patients in the SABR group; p=0·57). Palliative radiotherapy was more commonly delivered in the control group (21 [64%] of 33 patients) than in the SABR group (13 [20%] of 66 patients).

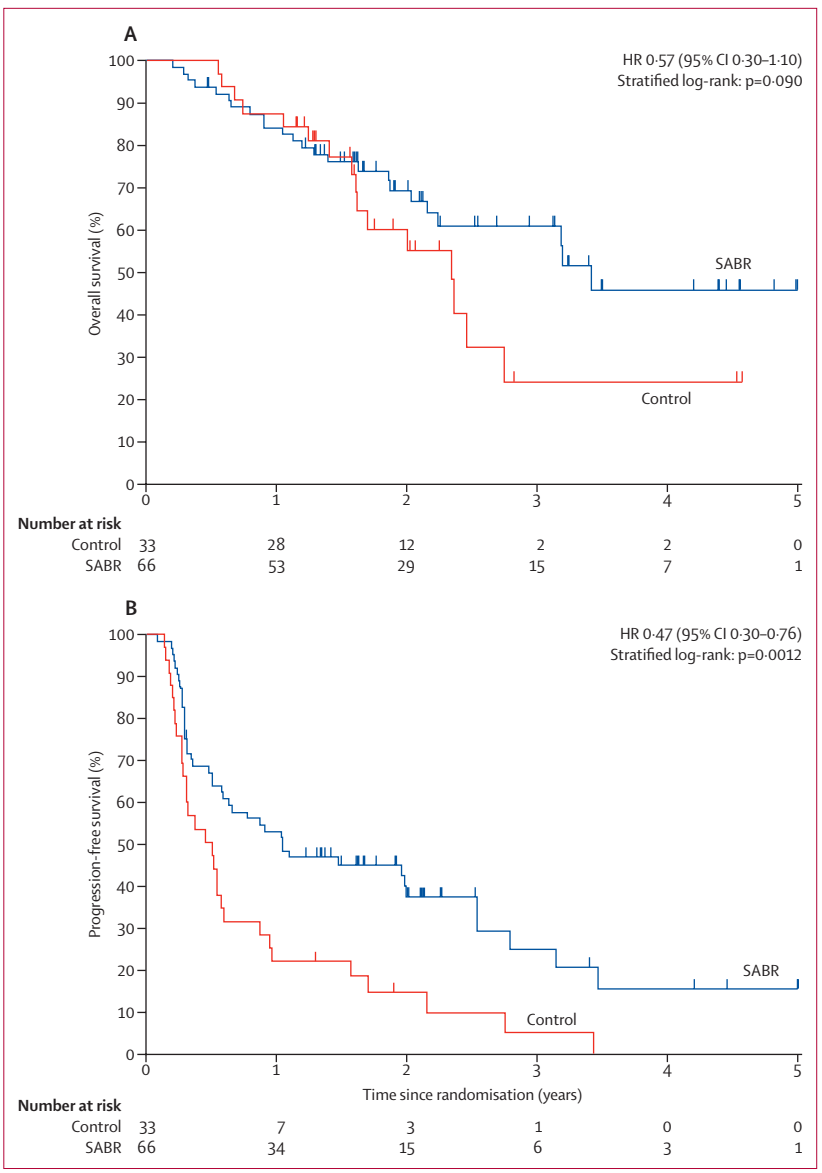

Figure 2: **Overall survival (A) and progression-free survival (B)**
SABR=stereotactic ablative radiotherapy. HR=hazard ratio.

Discussion

The use of ablative treatments in patients with oligometastatic cancers has been the subject of substantial debate.[5] Although the use of metastasis-directed surgery and stereotactic radiation has increased in the past 10–15 years,[8,9] the reliance on single-arm data of well selected patients without adequate controls has led to suggestions that the use of ablative treatments might be futile.[16,17] The main findings of the present study are that SABR was associated with a 13-month improvement in median overall survival and a doubling of median progression-free survival, at the cost of an increase in toxicity and a 4·5% treatment-related mortality in the SABR group. To our knowledge, the findings herein represent the strongest clinical evidence available in support of the oligometastatic state.

Several recent systematic reviews have examined the effect of ablative therapies in patients with oligometastatic cancers.[6,18–21] We did not identify any randomised trials in patients who were oligometastatic

	All patients (n=99)	Control group (n=33)	Stereotactic ablative radiotherapy group (n=66)	p value
Adverse event grade ≥2	55 (56%)	15 (46%)	40 (61%)	0·15
Related adverse event grade ≥2	22 (22%)	3 (9%)	19 (29%)	0·026
Adverse event associated with death (grade 5)	3 (3%)	0	3 (5%)	0·55
Fatigue*	..	..	..	0·45
Grade 2	6 (6%)	2 (6%)	4 (6%)	..
Grade 3	1 (1%)	1 (3%)	0	..
Dyspnoea*	..	..	..	1·00
Grade 2	1 (1%)	0	1 (2%)	..
Grade 3	1 (1%)	0	1 (2%)	..
Pain (any type)*	..	..	..	0·14
Grade 2	5 (5%)	0	5 (8%)	..
Grade 3	3 (3%)	0	3 (5%)	..

Data are n (%). *Treatment related.

Table 2: **Summary of adverse events**

in which the primary endpoint assessed a difference in overall survival between an ablative treatment group (eg, SABR or surgery) and a group that did not receive ablative therapy.

However, previous randomised trials have also provided evidence supporting the existence of an oligometastatic state, via secondary endpoints, in patients who were non-oligometastatic, and by using surrogate endpoints. In colorectal cancer metastatic to the liver through the portal venous system (ie, not in systemic circulation as in our current trial), the European Organization for Research and Treatment of Cancer 40004 trial[22] randomly assigned 119 patients with fewer than ten hepatic metastases to receive systemic therapy, with or without radio-frequency ablation. The primary objective was not a direct comparison of overall survival in the two groups, but to show a 30-month overall survival of at least 38% in the radio-frequency ablation group. The original report met the primary endpoint (30-month overall survival of 62% in the radio-frequency ablation group) but showed no difference in overall survival between the two groups, as the 30-month overall survival in the systemic therapy group was similar at 58% (p=0·22).[22] A secondary report after a median follow-up of 9·7 years detected a difference in overall survival in favour of the radio-frequency ablation group (HR 0·58, 95% CI 0·38–0·88; p=0·01).[23] Ablative therapies have also shown a modest overall survival benefit when surgery (median improvement 6 months[24]) or stereotactic radiation (median improvement 1·6 months[25]) were added to whole brain radiotherapy in the treatment of a single brain metastasis. However, these trials included patients with active systemic disease elsewhere and are not specific to oligometastases.

We identified three other randomised trials that evaluated surrogate endpoints. Two recent phase 2 randomised trials in patients with oligometastatic non-small-cell lung cancer showed a near-tripling of progression-free survival with the use of ablative therapies.[26,27] Additionally, a phase 2 trial in patients with oligometastatic prostate cancer showed an improvement in androgen-deprivation therapy-free survival.[28]

Outcomes in the SABR group of our study are congruent with results from non-randomised studies.[29,30] As one example, a multi-institutional analysis of 361 patients treated with SABR for one to five extracranial metastases from various primary tumours reported median overall survival of 47 months, median progression-free survival of 10 months, and a 3-year lesional control rate of 72%, similar to the results reported herein.[29]

In our trial, SABR was well tolerated in the majority of patients, with less than 30% having toxicity of grade 2 or worse. However, 4·5% of patients in the SABR group died as a result of toxicity, despite stringent dose constraints and a requirement for peer review of all radiation plans, which is higher than many retrospective studies. This finding suggests that SABR delivery should continue to focus on minimisation of toxicity and that the use of SABR in patients with more than five lesions should be done in the context of a clinical trial.

The overall survival findings herein meet the pre-specified endpoint for this phase 2 trial. However, phase 3 trials in single disease cohorts might be required to provide definitive evidence of an overall survival benefit in a broader spectrum of patients presenting with oligometastases, both metachronously (ie, after successful treatment of their primary tumour), and synchronously with their primary tumour. Such trials are ongoing, including a large cooperative group trial specific to each of lung cancer (NRG-LU002) and breast cancer (NRG-BR002). The progression-free survival benefit showed in the present study could be considered a definitive result, as a difference with a p value of less than 0·005 in a phase 2 randomised screening trial can be considered definitive in the absence of phase 3 data.[14]

Our findings should be considered in the context of the limitations of this trial. We included patients with multiple cancer types, a common approach in trials of stereotactic radiation for metastases.[25] We cannot exclude histology-specific differences in tumour biology that effect the benefits of stereotactic radiation. Histology-specific trials would be beneficial, but run the risk of poor accrual when patients with only one type of cancer can be enrolled to a specific trial. Although there were no major differences between groups in our trial with regards to baseline factors, the SABR group did contain a large number of patients with prostate cancer, which could have led to bias. Only a small number of patients in our trial had four to five metastases, limiting the value of our stratification factor, and robust conclusions about patients with more than three metastases cannot be drawn. The optimal dose and fractionation of SABR, and the optimal number of lesions treatable with acceptable risk remain unknown, and these topics should be

explored in future trials. The exact number of further cycles of systemic therapy, and the drugs used, could not be reliably ascertained as patients were often treated at other centres during the follow-up period. The QOL tool used herein (FACT-G) was of a general nature, reflecting that patients were expected to have varied QOL deficits based on the location of their metastases, but we might not have detected subtle organ-specific changes in QOL. However, an organ-specific QOL tool (eg, FACT-L for patients with lung lesions) would have been non-informative for patients without lesions in that location. The overall survival outcomes in this trial were much better than the a priori estimates of survival used in the sample size calculation, reflecting the shortage of previously published data for patients with oligometastases not treated radically. The better-than-expected survival in both groups suggest that oligometastatic cancers behave more indolently than previously appreciated, a finding similar to the conclusions from the European Organization for Research and Treatment of Cancer 40004 trial.[22]

Similar to other SABR trials, and radiation trials in general, this study was an unblinded, open-label trial. This study design can introduce bias, affecting patients (ie, by reporting higher QOL scores after randomisation to the experimental group) or physicians (by affecting their choice or timing of systemic therapy). Post-randomisation delivery of systemic therapy could not be ascertained as well as intended; this result is likely to reflect a desire by patients to receive palliative systemic therapies as close to home as possible. However, although we can never completely rule out such biases, we believe the risk to be small, for two reasons. Post-randomisation palliative treatments with systemic therapy or radiation were both numerically more common in the control group compared with the SABR group, and the magnitude of benefit in overall survival in this trial is also much longer than the benefits achieved with many types of systemic therapy. Finally, it is equally possible to envision a bias in the opposite direction (toward the null) in which patients randomised to the control group received more aggressive systemic therapy in light of not receiving SABR, reducing the apparent effect of SABR on overall survival in this trial. Each physician has a fiduciary duty to their patients to provide the best possible care, and to an extent we rely on physicians to do this duty and provide the highest level of care, regardless of the group to which a patient is randomly assigned.

The results of this trial have important implications for future trials of SABR for oligometastatic disease. The demonstration of a clear progression-free survival benefit might reduce the clinical equipoise of patients and physicians, hampering accrual to future trials. However, a phase 3 trial is required to conclusively prove an overall survival difference in patients with one to three metastases, and randomised trials are also required to define the maximum number of metastases wherein SABR still provides a benefit. The advent of immunotherapy adds to the uncertainty about SABR for oligometastatic disease. SABR has been suggested as a method of enhancing the effect of immunotherapy through immunological mechanisms, but randomised trials are required to support this concept. For any SABR trials, accrual might be most achievable in centres that have not yet adopted SABR or are not motivated to treat based on a progression-free survival benefit alone. Future studies should also aim to reduce SABR-related toxicity, and recognise that such toxicity might lead to crossing survival curves, potentially violating the assumptions of any Cox regression analyses and requiring alternative approaches.

In conclusion, in patients with a controlled primary tumour and one to five oligometastases, SABR is associated with a 13-month increase in overall survival and a doubling of progression-free survival. Further research should aim to provide support for the overall survival benefits for tumour-specific groups in formal phase 3 trials, and to develop biomarkers predictive of benefit with SABR to allow for better patient selection.

Contributors

DAP, SSenan, GBR, MLo, CH, BPY, and BA contributed to trial conception and design. AW and DAP contributed to data analysis. DAP, SSenan, and AW contributed to the initial draft of the manuscript. The first author (DAP) and statistician (AW) had full access to the data, vouch for the integrity of the data and the adherence to the study protocol, and are responsible for the decision to submit the manuscript. All authors contributed to data collection and interpretation, and revision of the manuscript for important content.

Declaration of interests

RO has received grant funding from Varian Medical Systems, unrelated to this research project. DS has received grant funding from Varian Medical Systems Inc, and honoraria from AstraZeneca, Bayer, and Merck, unrelated to this research project. AVL has received honoraria from Varian Medical Systems and AstraZeneca, unrelated to this research project. SSenan has received grant funding from ViewRay and Varian Medical Systems, and honoraria from AstraZeneca, Celgene, and MSD, unrelated to this research project. The other authors declare no competing interests.

Data sharing

The trial protocol did not include a data sharing plan, and therefore data from the trial will not be shared publicly as sharing was not included in the ethical approvals.

Acknowledgments

This study was funded by the Ontario Institute for Cancer Research and a London Regional Cancer Program Catalyst Grant.

References

1 Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E. Locally recurrent or metastatic breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012; **23** (suppl 7)**:** vii11–19.

2 Ettinger DS, Wood DE, Aisner DL, et al. Non-small cell lung cancer, version 5. 2017, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2017; **15:** 504–35.

3 Hellman S, Weichselbaum R. Oligometastases. *J Clin Oncol* 1995; **13:** 8–10.

4 Barney J, Churchill E. Adenocarcinoma of the kidney with metastasis to the lung cured by nephrectomy and lobectomy. *J Urol* 1939; **42:** 269–76.

5 Palma DA, Salama JK, Lo SS, et al. The oligometastatic state—separating truth from wishful thinking. *Nat Rev Clin Oncol* 2014; **11:** 549–57.

6 Ashworth A, Rodrigues G, Boldt G, Palma D. Is there an oligometastatic state in non-small cell lung cancer? A systematic review of the literature. *Lung Cancer* 2013; **82:** 197–203.

7 Utley M, Treasure T, Linklater K, Moller H. Better out than in? The resection of pulmonary metastases from colorectal tumours. 33rd International Conference on Operational Research Applied to Health Services (ORAHS 2007); Saint Etienne, France; July 15–20, 2007. 493–500.

8 Lewis SL, Porceddu S, Nakamura N, et al. Definitive stereotactic body radiotherapy (SBRT) for extracranial oligometastases: an international survey of >1000 radiation oncologists. *Am J Clin Oncol* 2017; **40:** 418–22.

9 Bartlett EK, Simmons KD, Wachtel H, et al. The rise in metastasectomy across cancer types over the past decade. *Cancer* 2015; **121:** 747–57.

10 Marquart J, Chen EY, Prasad V. Estimation of the percentage of US patients with cancer who benefit from genome-driven oncology. *JAMA Oncology* 2018; **4:** 1093–98.

11 Bernstein MB, Krishnan S, Hodge JW, Chang JY. Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach? *Nat Rev Clin Oncol* 2016; **13:** 516.

12 Timmerman RD, Herman J, Cho LC. Emergence of stereotactic body radiation therapy and its impact on current and future clinical practice. *J Clin Oncol* 2014; **32:** 2847–54.

13 Palma DA, Haasbeek CJ, Rodrigues GB, et al. Stereotactic ablative radiotherapy for comprehensive treatment of oligometastatic tumors (SABR-COMET): study protocol for a randomized phase II trial. *BMC Cancer* 2012; **12:** 305.

14 Rubinstein LV, Korn EL, Freidlin B, Hunsberger S, Ivy SP, Smith MA. Design issues of randomized phase II trials and a proposal for phase II screening trials. *J Clin Oncol* 2005; **23:** 7199–206.

15 Sharma MR, Stadler WM, Ratain MJ. Randomized phase II trials: a long-term investment with promising returns. *J Natl Cancer Inst* 2011; **103:** 1093–100.

16 Macbeth F. Avoid futile therapy. *Int J Radiat Oncol Biol Phys* 2017; **99:** 768.

17 Treasure T, Fallowfield L, Farewell V, et al. Pulmonary metastasectomy in colorectal cancer: time for a trial. *Eur J Surg Oncol* 2009; **35:** 686–89.

18 Vilela RA, Navarro NF, Faria ET, et al. Use of stereotactic body radiation therapy for oligometastatic recurrent prostate cancer: a systematic review. *J Med Imaging Radiat Oncol* 2018; **62:** 692–706.

19 Kucharczyk MJ, Parpia S, Walker-Dilks C, Banfield L, Swaminath A. Ablative therapies in metastatic breast cancer: a systematic review. *Breast Cancer Res Treat* 2017; **164:** 13–25.

20 Ost P, Bossi A, Decaestecker K, et al. Metastasis-directed therapy of regional and distant recurrences after curative treatment of prostate cancer: a systematic review of the literature. *Eur Urol* 2015; **67:** 852–63.

21 Fiorentino F, Hunt I, Teoh K, Treasure T, Utley M. Pulmonary metastasectomy in colorectal cancer: a systematic review and quantitative synthesis. *J R Soc Med* 2010; **103:** 60–66.

22 Ruers T, Punt C, Van Coevorden F, et al. Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). *Ann Oncol* 2012; **23:** 2619–26.

23 Ruers T, Van Coevorden F, Punt CJ, et al. Local treatment of unresectable colorectal liver metastases: results of a randomized phase II trial. *J Natl Cancer Inst* 2017; **109**.

24 Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 1990; **322:** 494–500.

25 Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* 2004; **363:** 1665–72.

26 Gomez DR, Blumenschein GR Jr, Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol* 2016; **17:** 1672–82.

27 Iyengar P, Wardak Z, Gerber DE, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a phase 2 randomized clinical trial. *JAMA Oncol* 2018; **4:** e173501.

28 Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. *J Clin Oncol* 2018; **36:** 446–53.

29 Hong JC, Ayala-Peacock DN, Lee J, et al. Classification for long-term survival in oligometastatic patients treated with ablative radiotherapy: a multi-institutional pooled analysis. *PLoS One* 2018; **13:** e0195149.

30 Collen C, Christian N, Schallier D, et al. Phase II study of stereotactic body radiotherapy to primary tumor and metastatic locations in oligometastatic nonsmall-cell lung cancer patients. *Ann Oncol* 2014; **25:** 1954–59.