

Treating asymptomatic lung metastases by resection or ablation has not been shown to benefit patients.

Fergus Macbeth¹

Lesley Fallowfield²

Elizabeth Treasure³

Irfan Ahmad⁴

Yan Zheng⁵

Tom Treasure⁶

¹Centre for Trials Research, Cardiff University, Cardiff CF14 4YS, UK

² Sussex Health Outcomes Research & Education in Cancer (SHORE-C), University of Sussex, Sussex, UK

³Oxford University Counselling Service, University of Oxford, Oxford UK

⁴ Radiation Oncology, Rajiv Gandhi Cancer Institute & Research Centre, New Delhi, India

⁵ Department of Thoracic Surgery, Henan Cancer Hospital/The affiliated Cancer Hospital of ZhengZhou University and Lung Cancer Institute of Sun Yat-Sen University, 127 Dong Ming Road. ZhengZhou. HN. 450008 P. R. China.

⁶Clinical Operational Research Unit, University College London, London UK

Correspondence to:

Full name Tom Treasure

Mailing address 111 Rue du Lieutenant Menard, 62164 Audresselles, France

Email: tom.treasure@gmail.co,

Phone: 00 33 6 08 94 13 11

Contributors and sources

Fergus Macbeth and Tom Treasure, as an oncologist and a surgeon treating cancer have lifelong clinical experience in the NHS. They have each led cancer trials including PulMiCC, worked with NICE and Cochrane, and have collaborated in disseminating evidence-based knowledge. Lesley Fallowfield is an academic psycho-oncologist involved in health outcomes research, research methods and cancer education, and co-chief investigator of the PulMiCC trial. Elizabeth Treasure is a breast cancer survivor. She is accredited by the British Association for Counselling and Psychotherapy since 1998 and works as a counsellor and CBT therapist in the University of Oxford. Irfan Ahmad and Yan Zheng (who was a principal investigator in the PulMiCC trial) face the dilemma of implementing Western consensus opinion in low- and middle-income contexts. Fergus Macbeth is the guarantor of the article.

Patient involvement

Elizabeth Treasure is in remission from breast cancer treated by three successive operations and chemotherapy. To avoid damage to her lungs, she declined radiotherapy offered as “belt and braces”. She contributes here to give a patient’s voice. Cancer doctors also commonly have a patient’s perspective in their own lives. Fergus Macbeth shared his wife’s “journeys” with breast and terminal lung cancer. Irfan Ahmad shared his grandfather’s struggle with terminal metastatic prostate cancer. Tom Treasure is in remission from prostate cancer after radical prostatectomy.

Conflicts of Interest

We have read and understood [BMJ policy on declaration of interests](#) and have no financial interests to declare:

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Standfirst

The authors argue that the surgical removal or ablation of lung metastases is not supported by any good evidence and represents ‘too much medicine’ and that the uncertain benefits and known risks should be more clearly presented to patients.

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The commonest site of systemic cancer metastases is in the lungs. Surgical resection has been in practice for over 50 years(1) and since 1995 it is increasingly justified by “framing”(2) a clinical state of oligometastasis as an “opportunity” for curative local treatment.(3, 4) (Box 1, Figure 1) In the NHS from 2005 to 2013 it has been estimated that 3434 patients had surgical metastasectomy.(5) Less invasive treatments — ablation by stereotactic ablative radiotherapy (SABR) or image guided thermal ablation (IGTA) — with the same objective are being used increasingly in Europe and North America. A 2020 updated guideline on colorectal cancer from The National Institute for Care Excellence (NICE) stated: ‘Consider metastasectomy, ablation or stereotactic body radiation therapy for people with lung metastases that are suitable for local treatment’, a recommendation citing one retrospective cohort study(6) rated as ‘Very Low Quality’ evidence, and “expert opinion” from a committee on which several members including its chair were actively engaged in treating metastases.(7) In 2021 the use of SABR for metastases was commissioned by NHS England(8) and in 2023 three international professional societies published clinical practice guidelines on the removal or ablation of lung metastases.(9, 10) These guidelines start with the assumption that removal of lung metastases from any cancer lengthens survival. Although lung metastases imply disseminated systemic disease, they in themselves rarely cause or contribute to death. Unlike bone or brain metastases, lung metastases are seldom symptomatic. Arguably, their continued presence may even guide treatment by providing a means of monitoring progression and response to treatment. We argue that existing clinical evidence does not support routine ablation or removal of lung metastases.

The patient perspective

When offered a local treatment for asymptomatic lung metastases, patients will expect their cancer team to give them information on the likelihood of longer survival, the effect on quality of life, and a discussion on the uncertainty of benefit. They will want honesty about the possible adverse effects and acceptance of their right to decline or defer a treatment, but still receive other appropriate care.(11)

Patients differ in how they prefer to make decisions about their own health care. A UK study has shown that some are *passive*, preferring to leave treatment decisions to the cancer team; the majority want a collaborative role, engaging in *shared decision-making with health professionals*; others, prefer to take an *active decision-making* role.(12) Most cancer patients want treatments that will help them live longer. Some want to be treated whatever the cost but others want to consider the trade-off between the hope of benefit and loss of enjoyment of life if treatments prove futile.(13) A large 2015 systematic review of 35 studies from around the world, encompassing 27,323 patients with a wide variety of conditions, has shown that they generally overestimated the benefits of treatment, screening and diagnostic tests and underestimated the harms of these interventions.(14)

Doctors often find it hard to be truthful about a poor prognosis.(15) A 2016 UK study of patients with a variety of advanced cancers receiving systemic treatment showed that some doctors prescribed treatment with novel drugs in the knowledge that the patients were unlikely to benefit.(16) Healthcare professionals need to make clear the proven rather than hoped-for benefits as well as the possible risks from lung metastasectomy but it may be difficult for both the patient and the medical team not to 'do something'.(17) A 2017 international survey of over a thousand radiation oncologists indicated clinicians' readiness to treat when the diagnosis "oligometastasis" is made.(18)

If cancer teams offer a treatment, patients may assume that there is evidence in support of that treatment modality. Most patients respond to information given both cognitively — considering what they have been told alongside what they have heard, which may be different — and also emotionally.(19) Optimism bias and intolerance of uncertainty can complicate issues further. Given the complexity of decision-making in modern medicine the cancer teams are in the powerful position of having knowledge, expertise and authority, in discussion with patients often experiencing powerful emotions. This can lead to pressure to 'do something' and make it hard to be truthful that nothing can be done of any proven use. Anxious patients abhor ambiguity and usually respond by making an emotional rather than a cognitively-based decision.(20)

Evidence of benefits and harms in removing lung metastases

A randomised controlled trial (RCT) 1982-93 of earlier detection of asymptomatic colorectal cancer recurrence found no benefit, and some detriment, perhaps due to harm from over treatment.(21) Meta-analyses of RCTs looking for benefit from intensification of surveillance have found the same.(22, 23)

RCTs comparing local interventions with observation alone for 'oligometastases' at various sites from a variety of cancers, are summarised in Table 1. Six reports included lung metastases(24-29) and two did not specify(30, 31). Six used progression-free survival(24-26, 28) or a surrogate — e.g. time to androgen deprivation treatment in prostate cancer(30) — as the primary outcome. Differences in progression-free survival may be misleading because in the treated arms the macroscopic sites of disease, where progression is most likely to be seen, were removed or ablated. Of those reporting significant improvement in overall survival two involved treating both the primary and metastatic sites and the use of systemic therapy.(24, 26) These cannot provide evidence of benefit from treating metastases alone. SABR-COMET investigated the use of SABR in 99 patients with various sites of metastases from a variety of primary cancers.(27) The intervention group had a higher proportion of better prognosis patients: those with a single metastasis and those with breast and prostate cancer. Two RCTs showed no survival benefit.(29, 31) All but one were Phase 2 RCTs, small studies, designed to be hypothesis-generating and they do not provide clear evidence of effectiveness. What we lack is a large-scale Phase 3 RCT showing that local treatment at any site is effective in improving overall survival. Patients should be told that.

PulMiCC (Pulmonary Metastasectomy in Colorectal Cancer (CRC)) was a study run 2010-2016 in the UK, Serbia, Italy and China(32) which recruited 512 patients with colorectal cancer and lung metastases. (Fig.2) The nested randomised controlled trial of 93 patients, comparing surgical removal of lung metastases with observation alone, ensured balance for prognostic features in the trial arms(33). There was no significant difference at any time point. (Fig.2 lower panel) The 25th centile and median survival (3.8 versus 3.5 years) were *longer* in the *no* metastasectomy arm.(29) The non-randomised cohort included 263 patients who had an elective metastasectomy.(34) Expert selection had systematically excluded patients with prognostic factors predictive of death within five years. The 60%

five-year survival matched the best results from observational studies in which patients were selected on the same well-known prognostic factors.(35, 36)

While PulMICC was recruiting the surgical consensus was that lung metastasectomy raised five-year survival from <5% to as much as 60%.(35, 36) This belief made randomisation in PulMiCC difficult. There were too few participants to prove non-inferiority(37), but the 93 participants gave 80% power to effectively rule out a difference greater than 26% in the proportion alive at 5 years, making the currently believed differences in five-year survival, attributable for operation, improbable.

The reasons for the paucity of randomisation in PulMiCC was investigated. In a sample of 155 patients from the three most actively recruiting UK sites. The cancer teams did not offer randomisation to half (78/155) of the patients of whom 77 (99%) were subsequently operated on. These were protocol violations undermining the power of the trial. Of 41 patients who wanted to choose their treatment, similar numbers (22 and 19) decided for and against an operation.(32) The near even split when patients chose shows an interesting equipoise not shared by the clinical teams.

The many retrospective studies(38) lack comparators and are subject to selection and guarantee-time biases.(39) Apparent longer survival is due to expertly-informed selection of patients with better prognosis. An analysis of observational data evaluated survival in 807 colorectal cancer patients who had undergone lung metastasectomy from 2010-2015. There was no significant survival difference compared with carefully matched controls.(40) This study did find a survival difference for resection of liver metastases which may be a special case due to filtration of hepatic portal venous return in the liver.

Lung metastasectomy and ablation are generally presented as “safe” interventions but there are risks of adverse events including death. Among electively operated patients in PulMiCC four died on the day of operation.(34) There were five further deaths in the first six months during which time there was only one death among patients who did not have an operation. So these five additional deaths were also likely to be treatment-related. In the SABR-COMET trial “Treatment-deaths occurred in three (4.5%) of 66 patients after

SABR, compared with none in the control group.”(27). Other documented adverse events include pneumothorax, pneumonitis and lung abscess.(27) Patients should be told of the harms of surgery and ablation.(41)

The National Institute for Health and Care Excellence (NICE) supported an NHS England programme to introduce SABR for metastases with an evaluation of its effectiveness. Doubts about likely benefit were published in the Royal College of Radiologists journal and BMJ(42, 43) and the PulMiCC protocol was changed to include SABR in the treatment arm. Nevertheless ‘evaluation’ was a simple registry(44) which reported only short-term survival — 79% at 2 years — similar to that in the control arm of PulMiCC. (Fig.2 lower panel) This lost opportunity to do an RCT is a concern. In this era of evidence-based healthcare and resource constraint we suggest that vested interests in clinical practice and the device industry may be the drivers of the increasing practice of ablating metastases.

Health professionals in low- and middle-income countries often look to higher income countries for guidance. However in these countries most people are uninsured and cannot afford private treatment, public-funded institutions have long waiting times for even establishing a diagnosis and there are other urgent priorities in cancer treatment and control.(45-48)

Conclusions

There may be long-term survivors whose metastases were truly limited and local treatments removed all residual disease leaving them cancer free. These instances may be memorable but are rare.(49) We suspect that long survivors are those with indolent disease. At present a large body of clinical opinion interprets the limited evidence more optimistically but a citation analysis showed that those leading opinion by publishing their results cited others of like mind and ignored contrary evidence.(50) Fig.3.

We believe that, as result of the commissioning of SABR for oligometastases by NHS England and the widespread promotion of surgery and ablation for lung metastases by clinical opinion leaders, increasing numbers of patients in the UK, Europe and North America are being treated, but it is impossible to glean from current data systems how

many. Without evidence of clinical effectiveness an intervention cannot be deemed cost effective. With the current pressures on cancer treatment, especially radiotherapy, in many countries it seems perverse to offer a treatment of uncertain benefit and irresponsible for professional bodies to endorse it when there are other pressing priorities. Those involved in making decisions about the availability and specific use of any treatment for lung metastases need to reflect on this.

Satisfying the hopes and expectations of patients and their families is all part of good medical care and must include realism, honesty and compassion.(13) For truly 'shared decision-making' patients need to know exactly how uncertain are the benefits and how real the risks of these interventions. Overall therefore the lack of good evidence of any survival benefit and documented risk of harm lead us to conclude that the removal or ablation of asymptomatic lung metastases is another example of 'too much medicine'.

BOX 1 Oligometastases

In 1995 the concept of an intermediate 'oligometastatic state' was proposed for patients with a 'few' metastases. It was suggested that cure might be achieved by surgical removal.(3) Recently techniques for ablation by radiation, heat or freezing have been developed and become popular because they are less invasive. Concurrently use of the term "oligometastatic disease" has increased significantly.(Fig.1). There is no agreed definition of how few metastases constitute 'oligometastases' – but usually less than five. In the opinion of the authors the term lacks any biological foundation and is a diagnostic term adopted to 'frame'(2) a therapeutic opportunity.(4)

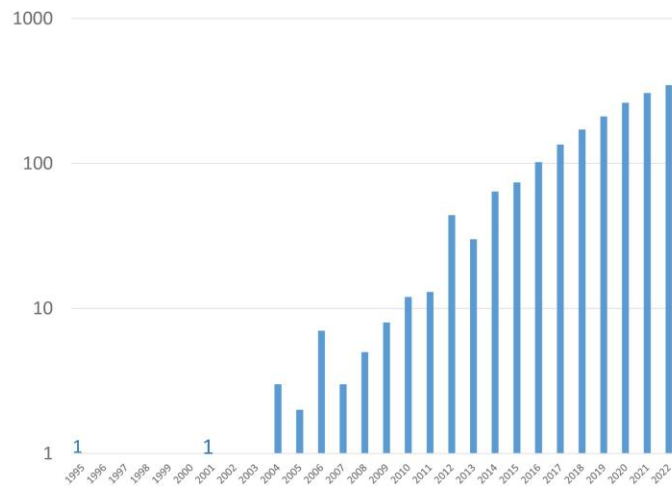


Figure 1 Use of oligometastasis/oligometastases/oligometastatic in the title of papers in the National Library of Medicine. Counts are shown on a log scale. The original hypothesis was published in 1995.(3) In the following 10 years it only appeared once more in a title in 2001 and then in single figures until about 10 years after it was proposed. In the last 15 years its use has grown exponentially. Note that 1 is zero on the log scale so the solitary papers in 1995 and 2001 are marked as “1”

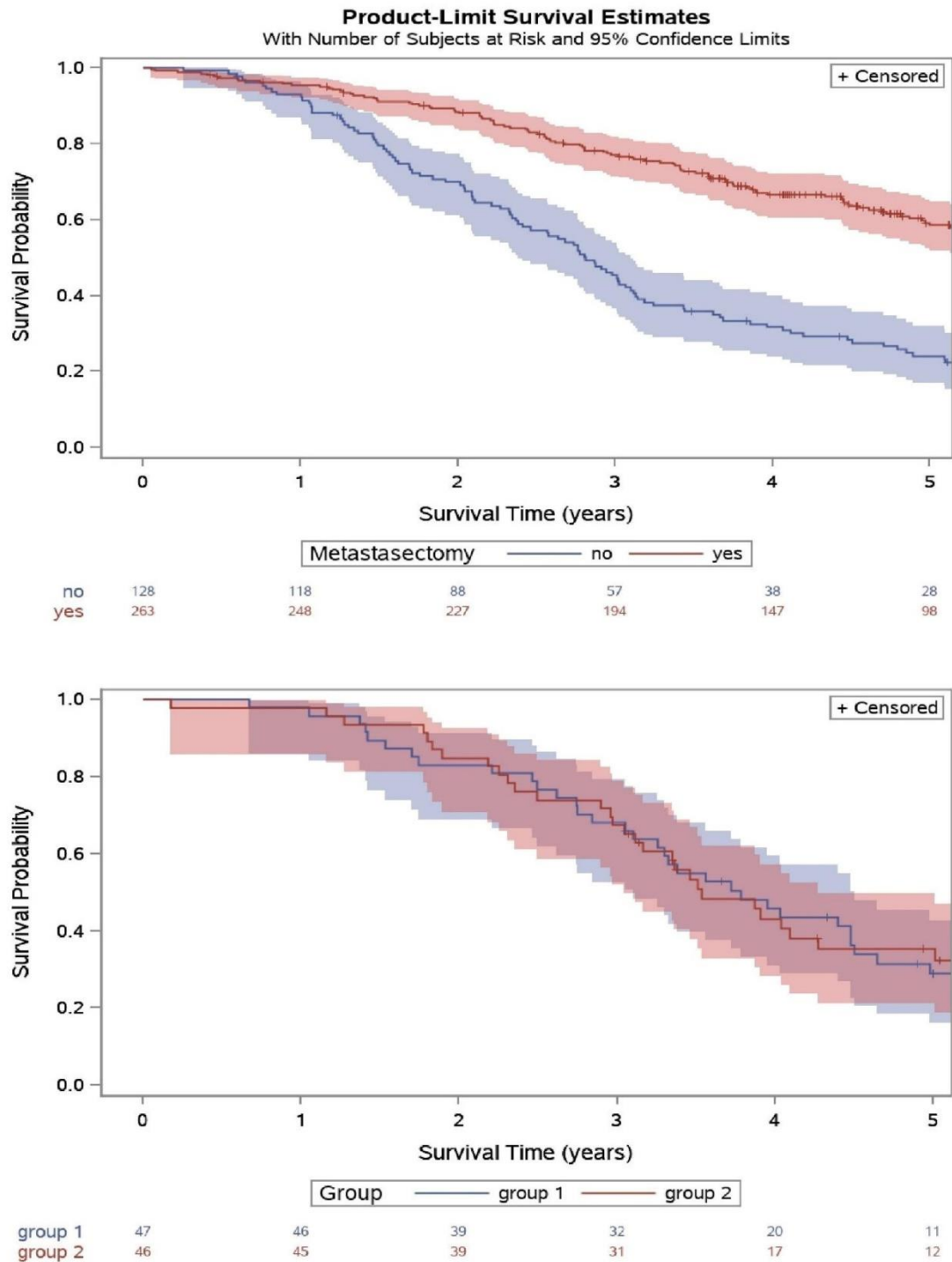


Figure 2. Of 484 patients with colorectal lung metastases in a prospect cohort study, with baseline and follow-up data collected to trial standards, 263 were selected for metastasectomy and 128 were not (upper panel). The survival of operated patients was comparable with the best reported “real world” outcomes. Those selected for surgery (a) had fewer metastases (b) more had non-elevation of the tumour marker carcinoembryonic antigen (CEA) (c) less advanced cancer stage at primary resection (d) less liver involvement (e) less performance impairment (f) nearer normal lung function and (g) they were younger.(34) Survival among patients not having metastasectomy was

not zero, or close to it, as is widely assumed. In the controlled trial (lower panel) there was no difference between the randomly assigned well-balanced arms. (29)

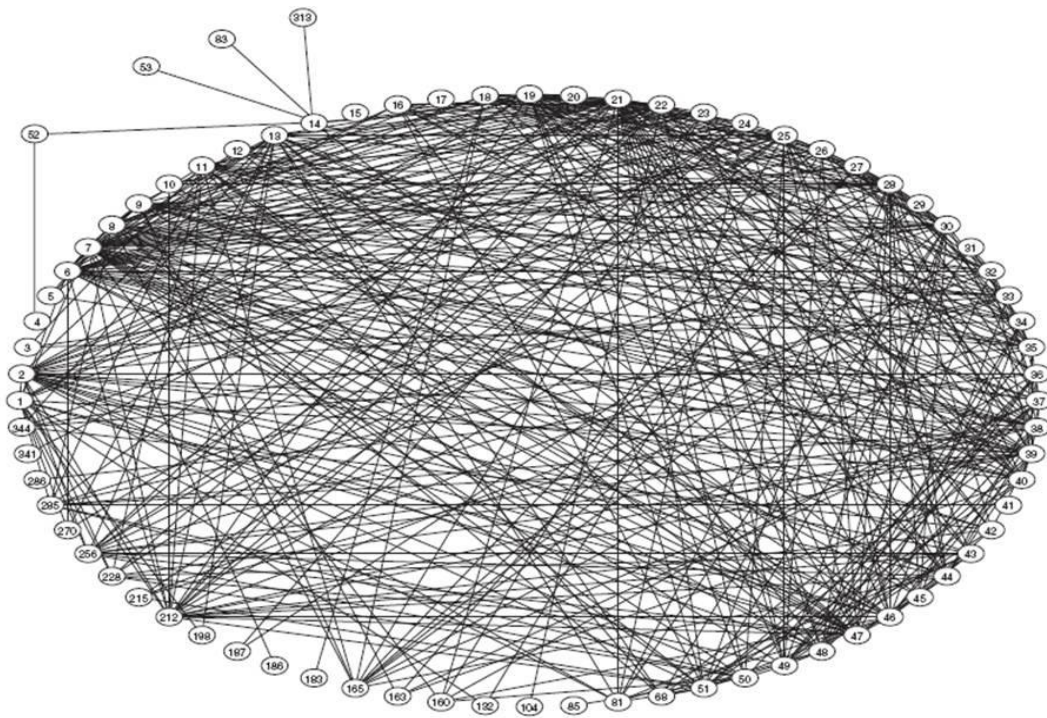


Figure.3

The network includes 51 papers reporting CRC lung metastasectomy clinical series, their numerous citations to each other, and other agreeing papers. (50) The image captures the extent of mutual citation. Four questioning papers on the periphery were little cited and soon forgotten. "The cumulative effect of citing more and more people who similarly agree with the author is to concretize the universality of the knowledge claim

Table Randomised trials of treatment with either surgery or radiotherapy to metastases. The control arm in all trials was appropriate management, either standard systemic treatment or observation and symptom control.

STUDY Countries	RCT PHASE	POPULATION	NUMBER	SITES OF METASTASES	TREATMENT ARM COMPARATOR	PRIMARY OUTCOME	MAIN FINDING	LIMITATIONS
Gomez et al 2019(15) USA/Canada	2	St IIB and IV NSCLC, stable disease after initial systemic treatment	49	11 different sites Lung 12%	Surgery or radical RT to primary and all metastases. Maintenance chemotherapy or observation	PFS	Significant improvement in PFS: median survival after intervention 14.2m (95% CI 7.4 to 23.1) versus 4.4m (95% CI, 2.2 to 8.3m) in controls p = 0.022	Trial closed early. Small numbers. Treatment to primary site not just metastases.
NCT02045446 Iyengar et al 2017(16) USA	2	St IV NSCLC, stable after initial chemotherapy	29	6 different sites Lung 13%	Maintenance chemotherapy+SABR to all sites of residual disease, including primary. Maintenance chemotherapy alone	PFS	Significant improvement in PFS: HR 0.304 (95% CI 0.113-0.815) Not powered for analysis of OS	Trial closed early. Small numbers. Treatment to primary site not just metastases.
SINDAS Wang et al 2022(17) China	3	St IV EGFR+ve NSCLC	133	Bone 70% Abdomen 18% Lung 8%	RT to all sites of disease, including primary, before systemic TKI treatment. TKI treatment alone	PFS	Significant improvement in PFS: HR 0.22 (95% CI 0.17 - 0.46) and OS: HR 0.44 (95% CI 0.28 - 0.68)	Treatment to primary site not just metastases.
SABR-COMET Palma et al 2019(18) Canada, Netherlands, Scotland, Australia	2	Multiple tumour types. Primary site treated and 'controlled'	99 (2:1 randomisation)	7 different sites Lung 53%	Standard palliative care treatment + SABR to all sites of metastasis. Standard palliative care treatment alone	OS	Significant improvement in OS reported but HR 0.57 (95% CI 0.30-1.10)	Imbalance in prognostic factors (number of metastases and proportion of breast and prostate patients) favouring intervention arm

ORIOLE Phillips et al 2020(19) USA	2	St IV Prostate. Recurrent hormone sensitive	54	Bone 38% Lymph nodes only 61%	SABR to all sites of metastasis. Surveillance	PFS	Significant improvement in PFS: HR 0.30 (95% CI 0.11- 0.81)	OS not reported
STOMP Ost et al 2018(20) Belgium	2	St IV Prostate. Recurrence after curative treatment	62	Lymph nodes 55% Others not specified	Surgical metastectomy or SABR to all sites of metastasis	ADT-free survival	Significant improvement in ADT-free survival: HR 0.60 (80% CI 0.40 - 0.90) No difference in HRQOL	OS not reported
PuMICC Milosevic et al 2020(21) UK, Serbia, China	3	St IV Colorectal	93	Lung 100%	Surgical metastectomy Surveillance	OS	No difference in OS: median survival after metastectomy 3.5 years (95% CI 3.1-6) versus controls 3.8 years (95% CI:4.6) or HRQOL	Closed early because of slow recruitment
NCT02364557 Chmura et al 2022(22) USA	2/3	St IV Breast. Primary site treated and 'controlled'.	125	Not described	Systemic treatment + Surgical metastectomy or SABR to all sites of metastasis. Systemic treatment alone	?PFS – not specified	No difference in PFS: HR 0.92 (70% CI 0.71, 1.17)	Closed early when no difference in PFS shown. Published in abstract only

Abbreviations: ADT: androgen deprivation therapy, CI: confidence interval, EGFR: epidermal growth factor receptor, HR: hazard ratio, HRQOL: health-related quality of life, m: months, NSCLC: non-small cell lung cancer, OS: overall survival, PFS: progression-free survival, RCT: randomised controlled trial, RT: radiotherapy, SABR: stereotactic radiotherapy, St: Stage

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