Title page

SABR for oligometastatic disease: great enthusiasm but scant evidence

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We believe that stereotactic radiotherapy (SABR) should not currently be offered to patients with asymptomatic 'oligometastases' outside a randomised controlled trial (RCT) with overall survival (OS) as the primary outcome and a 'no treatment' control arm. The opening of such a trial would remind multidisciplinary teams (MDTs) that clinical effectiveness has not been tested at the level routinely required for systemic cancer therapies(1) and offering the trial to patients would inform them that there is uncertainty. This would not preclude patients requesting ablation after adequate and impartial counselling. Nor would this exclude the use of SABR to treat symptomatic metastases if that was believed to be appropriate.

Ours is seen as a heretical viewpoint running counter to most published opinion and an increasing clinical practice around the world. (2-4) But it is based on evidence. The large prospective observational study in 391 patients shows that the difference in survival attributed to pulmonary metastasectomy for colorectal cancer is largely — maybe completely — explained by well-informed case selection. [Fig.1] The RCT alongside it, with two arms balanced for all risk factors, showed no difference at any time point.(5, 6) [Fig.1]

The routine clinical use of SABR for 'oligometastases' is not justified for two main reasons.

First there is no good reason to believe that 'oligometastases' are a distinct clinical entity rather than the extreme end of a skewed frequency distribution(7, 8). There is no agreed definition of 'oligometastases' 27 years on from Hellman and Weichselbaum's original proposal.(9). Metastases are detected by imaging techniques with finite resolution and it is usually the case that there are more lurking undetected. After all, the premise of adjuvant systemic therapy is that there may be

undetected systemic disease. Metastasectomy is a procedure defined by therapeutic opportunity rather than biology (7, 10) and with SABR and radiofrequency ablation (RFA) supplanting surgery those opportunities are increasing.

Secondly there is no trustworthy — that is controlled — evidence, after more than 40 years(11, 12) that policies of removing or ablating apparently solitary or few metastases improve overall survival or health-related quality of life – the two most important clinical outcomes in this situation. The great majority of all the published studies about metastasectomy are observational studies, mainly retrospective. They are all compromised by biases, in particular selection bias and guarantee time bias. And none would meet the criteria proposed by Glasziou and colleagues for accepting evidence of effectiveness from an observational study: a plausible mechanistic reason for the effect, a short time between the intervention and the effect, and a risk ratio of more than 10.(13) Without any truly comparable control patients who have not had any local intervention, none provide reliable evidence that these interventions actually prolong survival.

It has been suggested that there must be one or more molecular-pathological definitions (MPD) of an 'oligometastatic' disease sub-type for which local therapy improves survival. If there is no difference in survival overall, but patients with an apparently favourable MPD are split off and found to live longer, the remainder must fare commensurately worse. It is a zero sum game But it does not necessarily mean that the intervention was more effective in the longer surviving group. This is seen in many surgical studies of colorectal cancer. When patients in follow-up studies are divided in those with solitary rather than multiple metastases, with low rather than raised carcinoembryonic antigen levels, and with a longer rather than a shorter interval since primary resection, then one survival curve moves up and the other moves down. When they were similarly represented in the two groups in PulMiCC the very evident difference seen in the cohort disappeared. [Fig.1]

Perhaps the largest observational study that addresses SABR specifically is the recently published report of 'Commissioning through Evaluation' project commissioned by NHS England.(14) This records the short-term survival outcome of 1422 patients who received SABR for 'oligometastases' in 17 centres across England between 2015 and 2019. After a median follow up of only 13 months it reported a 2-year survival rate of 79%. This was described as a 'high level' of survival and led to the commissioning of the procedure across England. But these were highly selected patients: 71% with unimpaired performance status, 76% with a solitary metastasis, 29% with prostate cancer and 24% continuing systemic therapy. This survival rate is therefore not surprising, could be unrelated to the SABR and is comparable to that seen in the *untreated* controls in the PulMiCC RCT. Nearly 50% developed new metastases within two years, not an encouraging indicator of long-term survival or cure. The authors, and with them "Commissioning through Evaluation", by missing the opportunity to obtain control data in an RCT appear to have thrown the principles of evidence-based medicine, and all caution, to the wind. (Figure 2) One aim of the study was to enable to safe introduction of SABR to units not previously providing it but this would not have prevented an RCT being built into the evaluation with appropriate technical quality control.

Small RCTs such that of the widely cited Gomez et al(15, 16) that have progression-free survival (PFS) as the primary outcome are misleading. The trial of Gomez et al was closed early because 'there was a 99.46% probability of superiority of the LCT (local consolidative therapy) arm if the current trend continued'. This decision was based on PFS data with a median follow up of a little over a year. If all

detected monitorable metastases are ablated or removed in one arm it is inevitable that there will be a difference in PFS. PFS may be a useful surrogate measure that predicts for OS in the context of systemic therapy but cannot be for a local intervention such as SABR.

We know of only three RCTs with overall survival as an end point.

1. CLOCC randomised 119 patients with colorectal liver metastases, considered unresectable at the time, to have or not have RFA in addition to systemic treatments.(17) There was a significant difference in survival in the combined treatment arm only seen on prolonged follow-up when 11 patients were at risk. But there was an important difference in the numbers of metastases in the two groups leading us to doubt the reliability of their conclusion.(18)
2. SABR-COMET randomised 99 patients with a mixture of primary and metastatic sites 2:1 to SABR or not, with all patients receiving standard of care palliative treatment.(19) The trial was reported and widely cited as showing a significant benefit in OS. Again there was failure to balance the number of metastases and in this case the mix of pathologies was also different between the two arms.(20) These difference favoured the SABR treatment arm. Although the hazard ratio was O.57 the 95% confidence interval was 0.3-1.1 so if the arms had been balanced the marginal significance might well have been lost.
3. PulMiCC we have already mentioned. The 263 patients *selected* for metastasectomy had predominately solitary metastases, fewer had liver involvement or elevated carcinoembryonic antigen, and they were younger, had better lung function and performance status than the 128 electively not operated.(6) In contrast to CLOCC and SABR-COMET the PulMiCC RCT of 93 patients all these factors were well balanced. PulMiCC has been widely criticised for being 'too small' but it has a similar number of randomised patients as CLOCC and SABR-COMET.

If ablation were a new cancer drug it would not be approved by agencies such as the FDA, EMEA or NICE because of the lack of reliable evidence from large RCTs. SABR may have been shown to have efficacy in ablating the metastases at which it is aimed, although some recent studies suggest that the local recurrence rate may be as high as 22%.(21) But we are not convinced of its clinical effectiveness in improving the most important patient outcomes. Without that evidence cost effectiveness modelling studies , such as that of Kumar et al which is based on SABR_COMET, are unlikely to be reliable.(22) Also SABR is associated with a significant risk of harm including death.(23, 24)

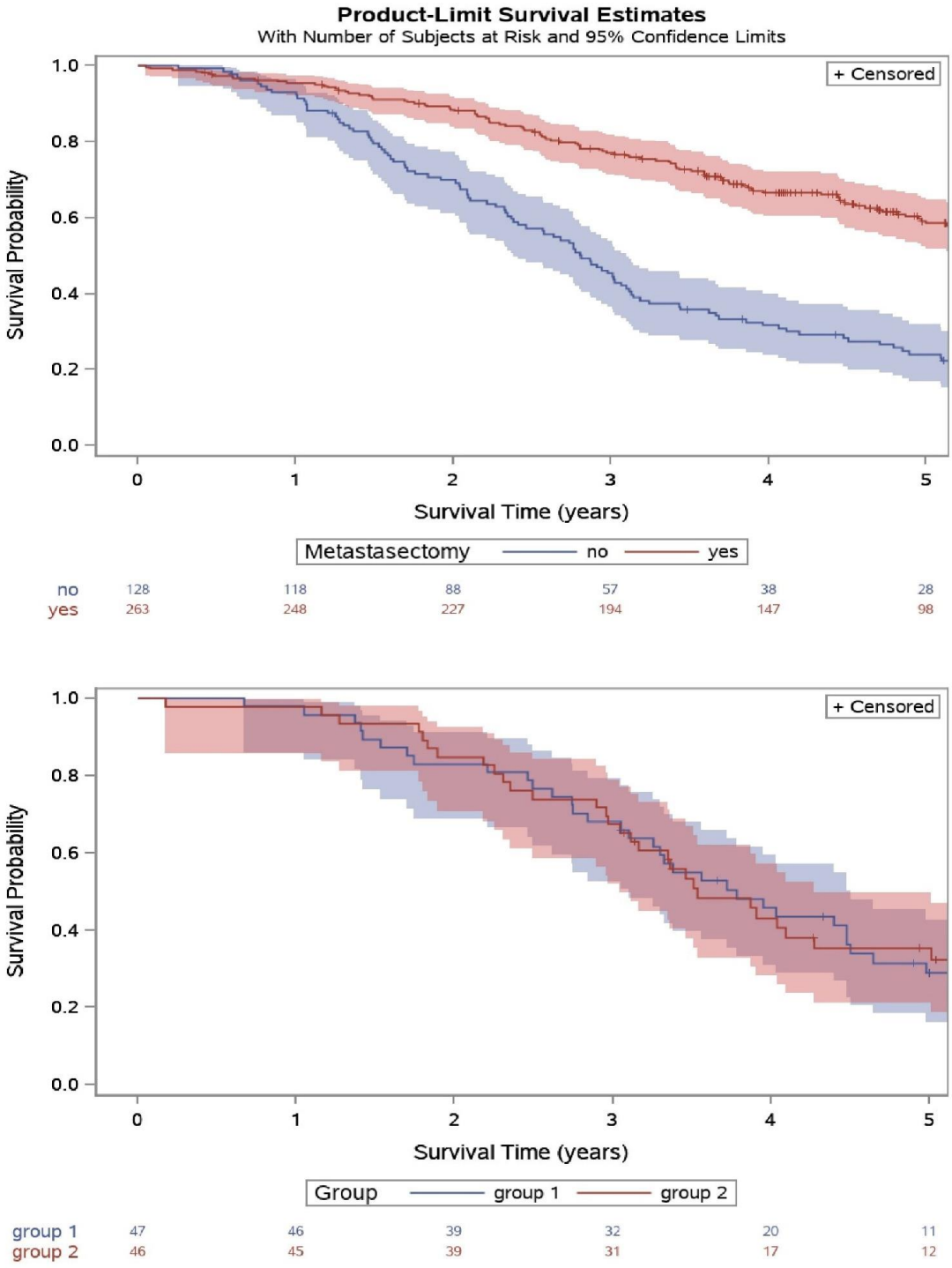
One or a very few *asymptomatic* metastases need local intervention only if treating them can be shown to improve overall survival. 'Watch and wait' may be an acceptable option for many patients when given an honest account of the likely risks and benefits. This was noted in PulMiCC. While overall recruitment was satisfactory the belief that survival would be zero without metastasectomy(12) made it very difficult for teams to not recommend operation. The independent data monitoring committee requested an analysis of the reasons. The three largest recruiting teams reported that where they had made the decision for the patients 77/79 (99%) were given metastasectomy. Among patients who made their own decision 19/42 chose to not have an operation (45%).(25) Well informed patients demonstrated equipoise and so it cannot be assumed that patients will all demand intervention.

So why is there such widespread belief in the effectiveness of metastasectomy whether surgical or by SABR or RFA despite this weak evidence? We believe it is because of technical and cognitive biases and the effect of motivated reasoning. We have already described the technical biases inherent in observational studies and in some of the RCTs. But beyond those there is clearly publication bias. All the studies mentioned above apart from PulMiCC were, despite their clear limitations, published in high impact oncology journals. PulMiCC was rejected by several mainstream journals before being published in a low impact online journal, 'Trials'.(25) This is not a complaint, just an observation.

The effect of cognitive biases on clinical decision-making is not often considered but influences the judgements of journal editors and peer reviewers, opinion leaders, individual health professionals and even policymakers. The key ones are:

- Confirmation bias: giving greater weight to observations and reports that support one's prior beliefs and discounting those that challenge them.
- Availability bias: remembering the more remarkable instances (such as a long-term survivor) and forgetting the commonplace (the many patients who have died).
- Authority bias: believing things said (often repeatedly) by authority figures and experts.

These together with the inevitable effects of academic, professional and financial competing interests result in motivated reasoning – 'the unconscious tendency of individuals to fit their processing of information to conclusions that suit some end or goal.'(26, 27) Those who advocate for and practice SABR for 'oligometastases' are clearly motivated to find reasons to support it and appear not to acknowledge the weaknesses in the evidence of its clinical effectiveness. Perhaps what we have written might make some think again but we are not optimistic. As Elizabeth Kolder explained in the New Yorker in 2017 'facts don't change our minds.'(28)



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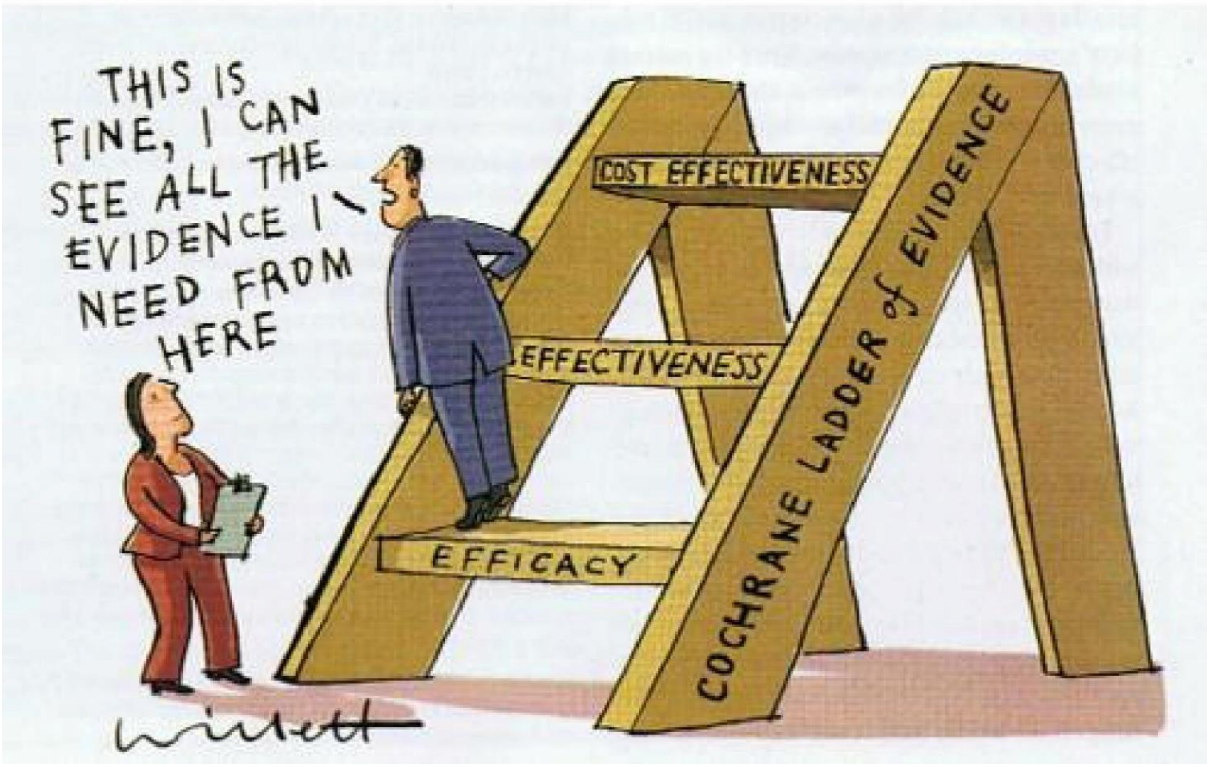
150 Figure 1: Survival plots for the three cohorts in PulMiCC. Above: those selected to have
151 metastasectomy or not. Below: those randomised - Group 1 no metastasectomy, Group 2
152 metastasectomy.



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154 Figure 2: The Cochrane Ladder of evidence. From Jarvinen TL, Sievanen H, Kannus P, Jokihaara J,
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156 http://www.ncbi.nlm.nih.gov/pubmed/21505222. Reproduced with permission.

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