

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 trial (RCT) that has overall survival (OS) as the primary outcome and a 'no treatment' control arm. This is clearly a heretical viewpoint running counter to most published opinion and an increasing clinical practice around the world. We will explain our reasons for taking this stance, which have been published widely already (1-3), and suggest why this practice is gaining so much traction.

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 phenomenon(4, 5). Secondly there is no trustworthy evidence, even after more than 40 years(6) of policies of removing or ablating apparently solitary or few metastases, that this intervention improves overall survival or health-related quality of life.

There is no agreed definition of 'oligometastases' 27 years on from Hellman and Weichselbaum's original proposal (7). According to the NCI Dictionary oligometastases are 'a small number of new tumors in one or two other parts of the body'. But there is no consensus as to how few this means and no convincing biological evidence or reasoning underpinning any proposed definition. The metastases are almost always detected by some imaging procedure such as CT +/- PET both of which have finite resolution. There is no reason to believe that if only one or two metastases are detected that there are not many more smaller ones lurking undetected. After all the premise of adjuvant systemic therapy for many apparently early cancers is that there may be undetected systemic disease. As we have pointed out before, metastasectomy is a procedure defined by therapeutic opportunity rather than biology (4) and with SABR and radiofrequency ablation (RFA) supplanting surgery those opportunities are clearly increasing.

What about the evidence? We will consider the evidence for all kinds of metastasectomy whether surgical or by ablation because they share a common principle. The great majority of all the published studies about metastasectomy are observational studies, mainly retrospective. However convincing the results may seem about the effect on OS 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 (8): a plausible mechanistic reason for the effect, a short time between the intervention and the effect, and a risk ratio of more than 10. Without any truly comparable control patients who have not had any local intervention, none provide reliable evidence that these interventions actually prolong patients' overall survival. As discussed below the most potent determinant of survival in groups of patients undergoing metastasectomy is case selection.

Perhaps the largest observational study that addresses SABR specifically is the recently published report of 'Commissioning through Evaluation' project commissioned by NHS England.(9) 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% PS0, 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 (see below). 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 1)

There have been RCTs published with ‘no treatment’ controls, almost all small phase II studies, but we only know three that have OS as the primary outcome. Small RCTs such that of the widely cited Gomez et al (ref)(10, 11) that have progression-free survival (PFS) as the primary outcome are misleading because if all detectable metastases are ablated or removed in one arm it is inevitable that there will be an improvement in PFS. The trial of Gomez et al was closed early because ‘there was a 99.46% probability of superiority of the LCT arm if the current trend continued’. This decision was based on PFS data but there was also an apparently significant improvement in OS. Although the two arms seem well balanced for major prognostic factors, with only 49 patients it is impossible to exclude chance variation producing the OS result. Phase II trials such as this should not change practice without confirmation in a large phase III RCT.

We know of three RCTs with OS as an end point.

CLOCC randomised 119 patients with colorectal liver metastases considered unresectable at the time to have or not have RFA in addition to systemic treatments.(12) 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.(13)

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.(14) The trial was reported and widely cited as showing a significant benefit in OS. But although the hazard ratio was 0.57 the 95% confidence interval was 0.3-1.1, not convincing evidence of effectiveness. 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.(15) These difference favoured the SABR treatment arm.

PulMiCC recruited 512 patients who were potential candidates for lung metastasectomy. 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.(16) All these factors were well balanced by minimisation in the nested RCT of 93 patients and there was no significant survival difference between those operated on and those not. (17) Figure 2 shows the survival of the two groups of non-randomised patients and of those in the RCT. PulMiCC has been widely criticised for being ‘too small’ but has a similar number of randomised patients as CLOCC and SABR-COMET. The RCT results clearly exclude a major difference in survival and, taken with the contemporaneous observational data from the wider study, illustrate the important effect of selection for favourable prognostic factors.

It is quite clear that if metastasectomy or 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 efficacy and ablate the metastases at which it is aimed but it has not been shown to have clinical effectiveness in improving patient outcomes. And without that evidence it cannot be cost effective because its use for ‘oligometastases’ generates opportunity costs in imaging and in

radiotherapy planning and treatment time – all resources currently under pressure in the NHS. And it is associated with a finite risk of harm including death. (Palma et al 2019)

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'.(18) 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.'(19, 20) 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.'(21)

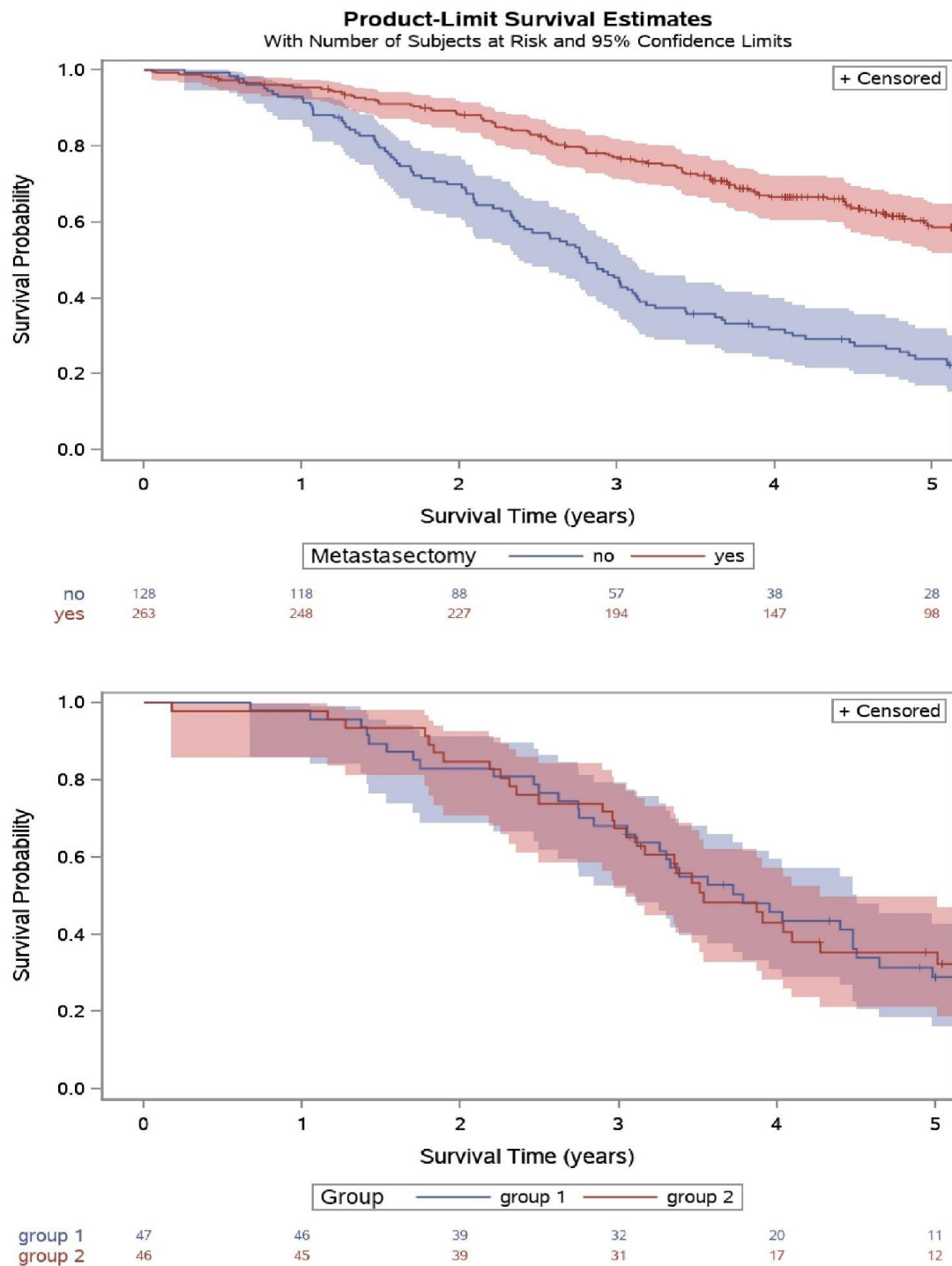


Figure 1: The Cochrane Ladder of evidence. From Jarvinen TL, Sievanen H, Kannus P, Jokihaara J, Khan KM. The true cost of pharmacological disease prevention. BMJ. 2011;342:d2175. <http://www.ncbi.nlm.nih.gov/pubmed/21505222>. Reproduced with permission.

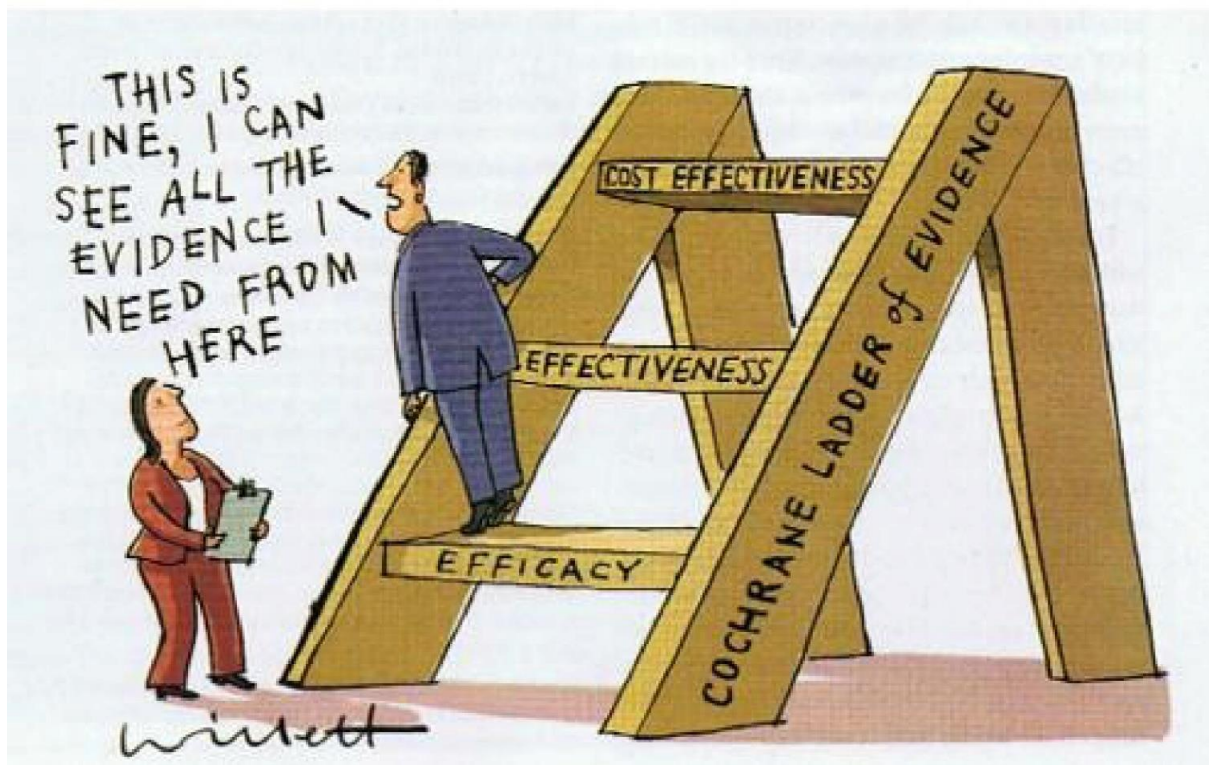


Figure 2: Survival plots for the three cohorts in PulMiCC. Above: those selected to have metastasectomy or not. Below: those randomised - Group 1 no metastasectomy, Group 2 metastasectomy

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