Editorial

Surgery and ablative techniques for lung metastases in the Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) trial: is there equivalence?

Tom Treasure

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

Correspondence to: Tom Treasure, MS, MD, FRCS, FRCP. Professor of Cardiothoracic Surgery; Clinical Operational Research Unit, University College London, London, UK. Email: tom.treasure@gmail.com.

Submitted May 05, 2016. Accepted for publication May 18, 2016.
doi: 10.21037/jtd.2016.06.50
View this article at: http://dx.doi.org/10.21037/jtd.2016.06.50

The Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) trial relies on a state of equipoise about any survival advantage from the treatment of lung metastases (1,2). It is accepted by the trialists that there may be rare instances when a lung metastasis is truly the only residual disease after treatment of the primary cancer and that its removal or ablation results in cure. Much more often the lung metastasis is the most readily visible manifestation of generalised blood borne dissemination and that becomes evident in the course of time. Most patient who have had lung metastasectomy go on to die of their cancer, even if they have survived the first 5 years.

Lung metastases themselves are rarely the cause of death or of symptoms. There are numerous confounding factors and there is a variable time course of disease progression towards death. Where the denominator data are available or can be deduced, surgical metastasectomy or ablation is undertaken in only about 3% of patients with colorectal lung metastases. These patients are selected on the basis of well-known prognostic features and the 'test of time' and are at the very best end of a wide distribution of survival. Therefore proof of oncological benefit requires a randomised controlled trial (RCT). Many interventions do not require RCT evidence and for them a firm conclusion can be based on intelligent observation (3) but treatment of lung metastases is not one of them. The grounds for uncertainty were introduced in the *British Medical Journal* in 2007 (4) and our analyses and the reason for doubt are summarised in *Thoracic Surgery Clinics* 2016 (5).

Increasingly patients are being offered ablation as an alternative to surgery with the implicit message that they are equivalent. The use of ablative techniques has relied on the assumption that surgical metastasectomy provides a survival advantage and that less invasive methods will achieve a similar effect but with less morbidity. If the prior assumption is insecure, then the ablative techniques may achieve radiological clearance but they are open to the same doubts about clinical effectiveness (6). Nevertheless they are being offered as alternatives to surgery. The PulMiCC trial management group decided that if they are to be regarded as equivalent, then they can and should be tested alongside surgery (7). Relative merits of one or another ablative method would require subsequent head to head comparisons in patients with metastases amenable to different methods of ablation. Such trials could be informed and powered by data obtained within PulMiCC. These alternatives therefore need to be understood. Within the space limits of this commentary they can only be briefly introduced but the citations are to authoritative technical and clinical reports published in the last few years.

Image guided thermal ablation (IGTA)

There have been several informative reviews of these techniques in the last few years in the treatment of lung metastases (8-11). The treatments are delivered usually by interventional radiologists and have in common that they destroy tissues by heating or cooling. The proximity of large blood vessels can make target temperatures difficult to achieve and the anatomical location will determine the

suitability of ablative techniques.

Radiofrequency ablation (RFA)

RFA is the longest standing alternative to surgery (12,13). RFA has been the subject of an authoritative review comparing outcomes with those for surgical metastasectomy. The authors conclude that trials are needed (14). There has been one RCT but that was in liver rather than lung metastases (15). The authors conclude "*The study shows that local tumor ablation by RFA in combination with systemic therapy results in an excellent survival, which however was also achieved in the control arm.*" This is of course an illogical statement because if there was no significant difference the 'result' cannot be attributed to RFA. So the bottom line is that in the only RCT found, the ablation had no beneficial effect on survival.

Cryoablation

Cryoablation for lung metastases has been studied in the ECLIPSE 'trial' which was a one arm prospective study (16). The authors report 1 year results for 40 patients. As with all follow-up studies of the treatment of lung metastases the patient were highly selected from those in the better end of a wide survival distribution and survival to 1 year was to be expected. It is not possible to attribute survival difference to the intervention.

Microwave ablation

Microwave ablation for lung metastases included in a series of 69 patients included 25 with lung metastastases (17). Again it is impossible to interpret the gain for the patients in the absence of control data.

Laser ablation

Laser ablation is in the arsenal but it appears to be little used as a percutaneous technique (11). Use of a laser is well established as a surgical tool at open surgery (18). There have been no controlled trials found.

Stereotactic ablative radiation (SABR) therapy for lung metastases

SABR is also known as stereotactic body radiation therapy (SBRT). There has been considerable recent interest in its use for lung metastases. The question was systematically reviewed and the authors pointed to the absence of evidence and raised the possibility that this was 'wishful thinking' (6). Despite the absence of evidence for any ablative techniques for metastases, SABR/SBRT has been much publicised for treatment of oligometastatic disease in the last year (19-21).

It should be noted that the term 'oligometastatic' was coined by radiation oncologists and is in fact an operational definition of advanced cancer where there are sufficiently few metastases for them to be treated by ablative techniques (22).

There are important differences for all of these methods when compared with surgery. After a surgical resection all the tissue is available for pathological examination which allows confirmation of diagnosis, proof of disease free margins (R0) and the opportunity to study tissue for any existing or future targeted or personalised therapies. Ablative techniques cannot be subjected to the same scrutiny of the tissues margins because all the biological evidence is destroyed in the process of ablation. Ablations are therefore not equivalent in a technical sense. However they may offer the same efficacy in terms of (I) the success of local control; (II) clinically useful palliation or (III) survival. The first two can be established by observational studies and that evidence may be sufficient but to show that survival is longer than it would have been in the natural course of events requires a controlled trial.

PulMiCC is open to recruitment internationally and it provides an opportunity to study the effects of different techniques in a pragmatic trial. Contributing teams may continue to follow their usual practice, selecting patients for treatment when it is considered appropriate, or to not operate or ablate where they think that it will not help. The basic premise of PulMiCC is that in this broad and multifaceted population of patients, if there is 'yes' to some and 'no' to others there must be some between them where there is equipoise about the decision. These can be recruited to the PulMiCC trials and offered random assignment.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Cancer research UK. A study looking at surgery to remove cancer that has spread to the lungs in people who have cancer that started in the bowel (PulMICC). Available online: www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-at-surgery-remove-cancer-spread-to-lungs-in-cancer-started-in-bowel-pulmicc
2. A Randomised Trial of Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC). Available online: https://clinicaltrials.gov/ct2/show/NCT01106261.
3. Glasziou P, Chalmers I, Rawlins M, et al. When are randomised trials unnecessary? Picking signal from noise. BMJ 2007;334:349-51.
4. Treasure T, Utley M, Hunt I. When professional opinion is not enough. BMJ 2007;334:831-2.
5. Treasure T, Macbeth F. Is Surgery Warranted for Oligometastatic Disease? Thorac Surg Clin 2016;26:79-90.
6. Palma DA, Salama JK, Lo SS, et al. The oligometastatic state - separating truth from wishful thinking. Nat Rev Clin Oncol 2014;11:549-57.
7. Treasure T, Macbeth F. Percutaneous Image Guided Thermal Ablation (IGTA) therapies are to be included in the interventional arm of the Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) trial to test if survival and quality of life are better than with intention to treat without intervention. Eur J Surg Oncol 2016;42:435-6.
8. Dupuy DE. Image-guided thermal ablation of lung malignancies. Radiology 2011;260:633-55.
9. Falk AT, Moureau-Zabotto L, Ouali M, et al. Effect on survival of local ablative treatment of metastases from sarcomas: a study of the French sarcoma group. Clin Oncol (R Coll Radiol) 2015;27:48-55.
10. Petre EN, Sofocleous CT, Solomon SB. Ablative and catheter-directed therapies for colorectal liver and lung metastases. Hematol Oncol Clin North Am 2015;29:117-33.
11. Quirk MT, Pomykala KL, Suh RD. Current readings: Percutaneous ablation for pulmonary metastatic disease. Semin Thorac Cardiovasc Surg 2014;26:239-48.
12. Gillams A, Khan Z, Osborn P, et al. Survival after radiofrequency ablation in 122 patients with inoperable colorectal lung metastases. Cardiovasc Intervent Radiol 2013;36:724-30.
13. Baba Y, Watanabe M, Yoshida N, et al. Radiofrequency ablation for pulmonary metastases from gastrointestinal cancers. Ann Thorac Cardiovasc Surg 2014;20:99-105.
14. Schlijper RC, Grutters JP, Houben R, et al. What to choose as radical local treatment for lung metastases from colo-rectal cancer: surgery or radiofrequency ablation? Cancer Treat Rev 2014;40:60-7.
15. 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.
16. de Baere T, Tselikas L, Woodrum D, et al. Evaluating Cryoablation of Metastatic Lung Tumors in Patients - Safety and Efficacy: The ECLIPSE trial - Interim analysis at 1-Year. Cardiol Rev 2015. [Epub ahead of print].
17. Belfiore G, Ronza F, Belfiore MP, et al. Patients' survival in lung malignancies treated by microwave ablation: our experience on 56 patients. Eur J Radiol 2013;82:177-81.
18. Moorcraft SY, Ladas G, Bowcock A, et al. Management of resectable colorectal lung metastases. Clin Exp Metastasis 2016;33:285-96.
19. 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 2015. [Epub ahead of print].
20. Hanna GG, Landau D. Stereotactic body radiotherapy for oligometastatic disease. Clin Oncol (R Coll Radiol) 2015;27:290-7.
21. Dearman C, van As N, Crellin A, et al. Surgery versus SABR for resectable non-small-cell lung cancer. Lancet Oncol 2015;16:e373-e374.
22. Treasure T. Oligometastatic cancer: an entity, a useful concept, or a therapeutic opportunity? J R Soc Med 2012;105:242-6.

Cite this article as: Treasure T. Surgery and ablative techniques for lung metastases in the Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) trial: is there equivalence? J Thorac Dis 2016;8(Suppl 9):S649-S651. doi: 10.21037/jtd.2016.06.50

