BJC

British Journal of Cancer (2015) 113, 1636 | doi: 10.1038/bjc.2015.331

Comment on: 'KRAS and BRAF mutations are prognostic biomarkers in patients undergoing lung metastasectomy of colorectal cancer.' Variation in survival associated with proto-oncongenes is not evidence for effectiveness of lung metastasectomy

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Sir,

The paper by Renaud *et al* (2015) begins and ends with acknowledgements that there has been no proof of effectiveness of pulmonary metastasectomy in colorectal cancer. The authors are correct. No difference in survival attributable to surgical removal of lung metastases has been shown in a controlled trial and yet it is regarded by them as 'steadily gaining acceptance'. Given the heterogeneity of patients with colorectal cancer, the variability in biology, the variety of treatments involved, and the variable time course between metastasectomy and death, a simple mechanistic cause and effect relationship cannot be derived from observational follow-up data (Glasziou *et al*, 2007; Fiorentino and Treasure, 2013a,b). Because of the lack of evidence for effectiveness the PulMiCC trial (Pulmonary Metastasectomy in Colorectal Cancer) seeks to answer that question (http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=9018).

The differences in survival according to whether the patients had V-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue (KRAS) or V-raf Murine sarcoma viral oncogene homologue B1 (BRAF) are striking as displayed in a Kaplan–Meier plot ($P<0.0001$). Survival of patients with KRAS is worse than those with wild type and for the 19 patients with BRAF is lower still. On the basis of these data it would seem to be foolhardy to offer metastasectomy to BRAF positive patients. That much seems clear. The study shows the influence of oncogenes on survival but these are likely to be general prognostic factors, not predictors of the effectiveness of lung metastasectomy itself (Simms *et al*, 2013).

These are highly selected patients collected over 14 years, barely more than one per month. They were selected because of their very limited disease: 'All of the patients were considered completely cured of their primary tumour at the time of thoracic metastasectomy, and all pulmonary metastases were metachronous' (Renaud *et al*, 2015). They were asymptomatic, fit for surgery and individually picked for operation after careful assessment including a judgement of their 'survivability' (Treasure *et al*, 2015) at the time of selection. They are out in the longer lived tail of the survival curve for patients with metastatic colon cancer (Utley *et al*, 2008) and a survival effect attributable to metastasectomy cannot be estimated from these data.

The statistical interpretation lacks critical insight. The authors performed an analysis for the well know factors predictive of early death after metastasectomy: more than one metastasis, any elevation of CEA, an interval shorter than 3 years since primary resection and involvement of mediastinal lymph nodes (Gonzalez *et al*, 2013). The failure of CEA and short intervals to show in this analysis is a simple example of a beta error. Adverse prognostic features have been systematically excluded by clinical selection so variation in prognosis attributable to them cannot be excluded (Utley and Treasure, 2008).

The choice of citations is also misleading. The publications cited for metastasectomy are follow-up studies (Treasure and Utley, 2007) from 1984 to 1996, reporting surgical series that closed >20 years ago. None of four systematic reviews were cited (Pfannschmidt *et al*, 2007; Fiorentino *et al*, 2010; Pfannschmidt *et al*, 2010; Gonzalez *et al*, 2013). It is well known that 'citation distortions create unfounded authority' (Greenberg, 2009). The problem has been well exemplified in lung metastasectomy for colorectal cancer (Fiorentino *et al*, 2011).

The authors conclude by saying: 'Lung metastasectomy of CRC is steadily gaining acceptance in the field of thoracic surgery, although it remains a subject of debate because of the absence of recent comparisons between simple follow-up and surgery'. There have been no randomised trials of metastasectomy in any tumour type and its effect on survival is therefore conjectural. But recently reported RCTs of the effect of intensive follow-up, with the intention of improving survival by operating on recurrent disease, show no survival benefit (Primrose *et al*, 2014; Treasure *et al*, 2014). This is indirect evidence casting further doubt on effectiveness of metastasectomy in colorectal cancer. It is hoped that the Cancer Research UK funded PulMiCC trial will bring some evidence to this important question.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Published online 15 September 2015