

Title

Comment on Moran's "Light at the End of the Tunnel". The Pulmonary Metastasectomy in Colorectal Cancer study sheds some light on the question.

Short running head

Pulmonary Metastasectomy in Colorectal Cancer

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The Editorial about resection of colorectal cancer (CRC) peritoneal metastases referred to the Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) randomised controlled trial (RCT)<sup>1</sup> only to dismissed it.<sup>2</sup> We write to update the citation<sup>3</sup> and summarise some published data from the full PulMiCC study.<sup>4 5</sup>

Recruitment reached 512 patients but the Society of Thoracic Surgeons published consensus — that without metastasectomy survival would be zero<sup>6</sup> — led to the majority of patients (263) being *selected for* metastasectomy.<sup>4</sup> The 22% five-year survival among 128 unoperated patients refutes the zero assumption ( $P < 0.001$ ).<sup>4</sup> All prognostic factors favoured the operated patients: fewer (31% vs 65%) had solitary metastases, elevated carcinoembryonic antigen, liver involvement and impaired performance status. They were younger with better lung function. Five-year survival (~60%) was comparable with the best of “real world” outcomes.<sup>7</sup> For the randomised patients prognostic factors were excellently balanced in the two arms of the nested RCT. There was no survival difference at any time point.<sup>3</sup> The number randomised (N=93) precluded proof of non-inferiority but the generally believed large benefit can be confidently refuted.<sup>8</sup>

Moran cited median survival of 42 months in PRODIGE as evidence for effectiveness of peritoneal resection but it was hyperthermic intraperitoneal chemotherapy (HIPEC) that was under test. There were no *unoperated* patients.<sup>9</sup> Without well-balanced controls there is no proof of benefit. Similar median survivals were seen in PulMiCC RCT: 42 and 45.6 month, treated and control respectively.<sup>9</sup> Selection for inclusion and guarantee time bias play a major part in such “better than expected” survival figures.<sup>10 5</sup>

## References

1. Treasure T, Farewell V, Macbeth F, et al. Pulmonary Metastasectomy versus Continued Active Monitoring in Colorectal Cancer (PulMiCC): a multicentre randomised clinical trial. *Trials* 2019;20(1):718. doi: 10.1186/s13063-019-3837-y [doi];10.1186/s13063-019-3837-y [pii]
2. Moran BJ. Detecting and Managing Colorectal Peritoneal Metastases: Some "Light at the End of the Tunnel". *Dis Colon Rectum* 2022;65(3):301-03. doi: 10.1097/DCR.0000000000002302 [published Online First: 2021/11/15]
3. Milosevic M, Edwards J, Tsang D, et al. Pulmonary Metastasectomy in Colorectal Cancer: updated analysis of 93 randomized patients - control survival is much better than previously assumed. *Colorectal Dis* 2020 doi: 10.1111/codi.15113 [published Online First: 2020/05/11]
4. Treasure T, Farewell V, Macbeth F, et al. The Pulmonary Metastasectomy in Colorectal Cancer cohort study: Analysis of case selection, risk factors and survival in a prospective observational study of 512 patients. *Colorectal Dis* 2021;23(7):1793-803. doi: 10.1111/codi.15651 [published Online First: 2021/03/31]
5. Treasure T, Farewell V, Macbeth F, et al. The Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) burden of care study: Analysis of local treatments for lung metastases and systemic chemotherapy in 220 patients in the PulMiCC cohort. *Colorectal Dis* 2021;23(11):2911-22. doi: 10.1111/codi.15833 [published Online First: 2021/07/27]
6. Handy JR, Bremner RM, Crocenzi TS, et al. Expert Consensus Document on Pulmonary Metastasectomy. *Ann Thorac Surg* 2019;107(2):631-49. doi: S0003-4975(18)31680-1 [pii];10.1016/j.athoracsur.2018.10.028 [doi]
7. Schirren J, Schirren M, Lampl L, et al. Surgery for pulmonary metastases: quo vadis? *Eur J Cardiothorac Surg* 2017;51(3):408-10. doi: 3052477 [pii];10.1093/ejcts/ezw441 [doi]
8. Fiorentino F, Treasure T. Sample size calculations for randomized controlled trials and for prediction models. *Colorectal Dis* 2021;23(1):316-19. doi: 10.1111/codi.15489 [published Online First: 2020/12/16]
9. Quenet F, Elias D, Roca L, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2021;22(2):256-66. doi: 10.1016/S1470-2045(20)30599-4 [published Online First: 2021/01/22]
10. Giobbie-Hurder A, Gelber RD, Regan MM. Challenges of guarantee-time bias. *J Clin Oncol* 2013;31(23):2963-9. doi: 10.1200/JCO.2013.49.5283 [published Online First: 2013/07/10]