

## Resection of asymptomatic primary tumour in unresectable stage IV colorectal cancer: time to move on from propensity matched scores to randomized controlled trials

Colorectal cancer (CRC) remains a major global disease burden with over 1.2 million new cases each year – about half of those who get the disease will die within 5 years of diagnosis<sup>1</sup>. At the time of diagnosis, some 20% already present with stage IV disease, of which only a minority (15–20%) are amenable for attempt at curative resection (usually for liver metastasis), either as an upfront combined resection or as a staged approach with or without combinations of neoadjuvant systemic treatment<sup>2</sup>. Despite several improvements in systemic therapy and modern surgical strategies for attempts at cure, the majority of patients with stage IV disease are unresectable and only amenable to palliative strategies. For patients who have a symptomatic primary (e.g. obstruction, perforation or bleeding) a surgical resection or stoma may be warranted if other attempts at bypassing the problem or as a bridge to later surgery is not possible (e.g. endoscopic stenting)<sup>3</sup>. In contrast, for those patients with stage IV disease having an asymptomatic primary tumour (either in colon or rectum) the role and potential benefit (if any) – and, notably, also the potential harm – of resection of the primary tumour has been much more controversial. Thus, the debate continues<sup>4–7</sup>.

Contestants against primary resection would argue that palliation is not possible if the patient does not have any symptoms to “palliate” and the limiting factor for survival is control of the metastatic disease and so systemic therapy should be prioritized. Proponents for resection of the primary tumour argue that reducing the tumour load reduces the disease burden and even disease progress, makes systemic therapy more effective and pre-emptively manages potential complications from occurring. Both sides may be right – and wrong.

Indeed, a more aggressive approach to unresectable stage IV disease was seen in the past, with every 3 in 4 patients having the primary tumour resected, with a drop to just over every one in two being resected in the latter time period<sup>8,9</sup>. Of notice, as the resection rates have dropped, the survival rates doubled from 8.6% in 1988 to 17.8% in 2009 ( $P < 0.001$ )<sup>9</sup>. However, using the same datasets, other investigators have come to different conclusions regarding resections of asymptomatic primary tumours in otherwise unresectable stage IV colorectal cancer<sup>10</sup>. Notably, these cohort studies sampled over longer time periods are biased towards the multiple factors that changed with the time and development in diagnostics, management and available systemic treatment that have not been controlled for in the comparative analyses.

In this issue of the *Journal*, a nationwide cohort study from the Netherlands investigated survival after primary tumour resection in unresectable stage IV CRC<sup>11</sup>. Using a propensity

score matched approach, they found a survival benefit for those who underwent primary tumour resection ( $n=2746$ ) compared to systemic chemotherapy ( $n=3345$ ). When matched by propensity scores in a 1:1 fashion, resection was beneficial for survival when combined with systemic therapy both before and after resection, yet resection upfront with subsequent chemotherapy proved to be best. The authors conclude that this treatment should be entertained more often as an option, even for those with no symptoms from the primary tumour.

While the findings may truly be so that primary tumour resection provides for a survival benefit, several points need to be considered before jumping to conclusions. Notably, propensity scores can be used in several ways<sup>12</sup>, of which propensity score matching is one. This involves a matched modelling of assembled pairs of two interventions (in this case resection or no resection) to selected baseline characteristics in an attempt to reduce bias. It works similar to a randomized trial, except it is not randomized and it is not a trial. Propensity score matching is still based on matching of the available, chosen data for matching. In the current study, a total of 1737 (28.5%) of the patients were not ‘matchable’ (one third resected primary, two thirds non-resected) and thus excluded. As the authors matched pairs based on year of diagnosis, age, tumour location, morphology and number of organs with metastases (1 or >1), several factors that may influence survival were not matched for. Notably, presence of comorbidity (e.g. ASA score, Charlson-Deyo score, presence of any organ function deficits etc) or functional status (e.g. ECOG status level) were not available and thus not controlled for. Also, TNM stage was not matchable due to the nature of those non-resected (lacking a pTNM status). Thus, it may still be so that those who received surgery up front were deemed fitter and more likely to tolerate a surgical procedure. Or, alternatively, had less extensive disease overall.

Further, one needs to scrutinize the choice of endpoint in the current setting of non-curable disease. When there are no symptoms to alleviate, one may question if overall survival is the best outcome measure to address. The added months of survival may truly be valuable for the individual patient, but one should consider at which risk and at what price this comes. For one, the current study had a 30-day mortality rate in the resected patients at 9%, which was similar for the systemic therapy group. These numbers are staggering, and far beyond those seen in any controlled trial of systemic therapy. However, they may actually reflect the truth in a real-life setting and, also, points to the risk of adversary effects of “just doing something” in a palliative setting. Given that all emergency resections (known

**Table 1.** Overview of ongoing randomized controlled trials for resection of primary tumour in unresectable stage IV colon or rectal cancer.

Trial/name	Origin	Trial <sup>3</sup>	Inclusion age	Primary outcome	sample (n)	Est. Completed, date
SYNCHRONOUS	Germany, Austria	ISRCTN30964555	≥18 years <sup>1</sup>	OS, 3 yrs	800	July 2019
CAIRO4	Netherlands, Denmark	NCT01606098	≥18 years	OS, 5 yrs	360	August 2020
CCRe-IV	Spain	NCT02015923	≥18 years	OS, 2 yrs	336	November 2016
Korean multicenter	Korea	NCT01978249	20-90 yrs <sup>2</sup>	OS, 2 yrs	480	April 2018
China multicenter	China	NCT02149784	18-75 years	OS, 3 yrs	480	July 2019

<sup>1</sup>for colon cancer primary only; rectal cancers are excluded

<sup>2</sup>colon and upper rectum cancers

<sup>3</sup>from either registry ISRCTN ([www.isrctn.com](http://www.isrctn.com)) or NCT ([www.Clinicaltrials.gov](http://www.Clinicaltrials.gov)). OS denotes Overall survival

for a very high perioperative mortality) were excluded, the rate of short-term deaths in what should be considered 'elective' surgery is considerable. For patients aged over 75 years, the 30-day mortality rate was even higher at 15%. The message is that either 'palliative' approach comes at a high risk of short-term death, knowing that these patients were likely deemed better performers than the 'best supportive care' candidates that were not included in the analyses. So, with a high risk of death (one in ten) for a relatively short survival benefit (of a few months) in otherwise asymptomatic patients, one may question if overall survival is the correct endpoint to consider. Further, doing landmark analysis of survivors beyond a 6 months period (during which time a considerable number of patients die) further skews the data towards favourable reporting of survivor bias (you have to be alive in order to live longer). Further, perioperative risk for anastomotic leaks is higher in patients with metastatic disease<sup>13</sup>, and this again strongly influences survival<sup>14</sup>.

Arguably, quality of life may be far more important in this patient group, whose longevity is limited but for whom symptom control is paramount. Data on QoL are very limited but may improve with surgical resection, as demonstrated in a very small (n=24), uncontrolled, cohort study<sup>15</sup>. No other studies have reported QoL data in this setting thus far<sup>16</sup>, which only testifies to the glaring lack of research in this field<sup>17</sup>.

Several systematic reviews have been conducted<sup>16,18,19</sup>. Based on limited data from few and heterogeneous studies with considerable reported bias, the median survival is reported at 15.2 months (range 10-30.7 months) in the resection group and 11.4 months (range 3-22 months) in the non-resection group, with a notable overlap in the reported ranges for both. This likely reflects the poor selection of appropriate candidates and a huge case-mix in disease burden, functional status and additional comorbidity. Also, a number of previously reported propensity matched studies have shown a variation in patient selection and outcomes<sup>10,20-25</sup>, but presents a reserved but favourable view on primary tumour resection for selected patients. As evidenced from one recent metaanalysis of heterogeneous studies, the patients that may benefit most from primary tumour resection are those who are young, fit, have a good performance status, and have minimal systemic disease<sup>19</sup>. However, the propensity

matched cohort and their associated findings have reached a limit in terms of information for decision-making. It is now time to move on to randomized trials.

Indeed, a lack of randomized controlled trials (RCTs) in this area is what keeps the debate alive. Thus, several ongoing randomized trials (the German-Austrian SYNCHRONOUS<sup>26</sup> trial, the Dutch-Danish CAIRO4<sup>27</sup> trial, the Korean multicenter trial<sup>28</sup>, and the Chinese trial<sup>29</sup>) and their expected results are much needed (Table 1). In addition to survival outcomes, at least three of the RCTs have stated QoL as secondary outcomes, and as such these measures will be of additional value for decision-making for both patients and caregivers alike.

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## References

- Brenner H, Kloor M, Pox CP. Colorectal cancer. *Lancet (London, England)*. 2014;383(9927):1490–1502.
- Adam R, de Gramont A, Figueras J, et al. Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus. *Cancer treatment reviews*. 2015;41(9):729–741.
- Soreide K. Emergency management of acute obstructed left-sided colon cancer: loops, stents or tubes? *Endoscopy*. 2013;45(4):247–248.
- Patel S, Chang GJ. Primary Tumor Resection in Metastatic Colorectal Cancer: Please Pass the Salt. *JAMA oncology*. 2015;1(9):1213–1214.
- Chang GJ. Primary tumor resection in stage IV colorectal cancer: the debate continues. *Diseases of the colon and rectum*. 2011;54(8):919–920.
- Mik M, Dziki L, Galbfach P, Trzcinski R, Sygut A, Dziki A. Resection of the primary tumour or other palliative procedures in incurable stage IV colorectal cancer patients? *Colorectal disease: the official journal of the Association of Coloproctology of Great Britain and Ireland*. 2010;12(7 Online):e61–67.
- Cellini C, Hunt SR, Fleshman JW, Birnbaum EH, Bierhals AJ, Mutch MG. Stage IV rectal cancer with liver metastases: is there a benefit to resection of the primary tumor? *World journal of surgery*. 2010;34(5):1102–1108.
- Shapiro M, Rashid NU, Whang EE, et al. Trends and predictors of resection of the primary tumor for patients with stage IV colorectal cancer. *Journal of surgical oncology*. 2015;111(7):911–916.
- Hu CY, Bailey CE, You YN, et al. Time trend analysis of primary tumor resection for stage IV colorectal cancer: less surgery, improved survival. *JAMA surgery*. 2015;150(3):245–251.
- Tarantino I, Warschkow R, Wornik M, et al. Prognostic Relevance of Palliative Primary Tumor Removal in 37,793 Metastatic Colorectal Cancer Patients: A Population-Based, Propensity Score-Adjusted Trend Analysis. *Annals of surgery*. 2015;262(1):112–120.
- t Lam-Boer J, Van der Geest L, Verhoef C, Elferink M, Koopman M, de Wilt J. Palliative resection of the primary tumor is associated with improved overall survival in incurable stage IV colorectal cancer: a nationwide population-based propensity-score adjusted study in The Netherlands. *Int J Cancer*. 2016;in press:in press.
- Haukoos JS, Lewis RJ. The Propensity Score. *Jama*. 2015;314(15):1637–1638.
- Kaser SA, Mattiello D, Maurer CA. Distant Metastasis in Colorectal Cancer is a Risk Factor for Anastomotic Leakage. *Annals of surgical oncology*. 2016;23(3):888–893.
- Smith JD, Butte JM, Weiser MR, et al. Anastomotic leak following low anterior resection in stage IV rectal cancer is associated with poor survival. *Annals of surgical oncology*. 2013;20(8):2641–2646.
- Tan WJ, Chew MH, Tan IB, et al. Palliative surgical intervention in metastatic colorectal carcinoma: a prospective analysis of quality of life. *Colorectal disease: the official journal of the Association of Coloproctology of Great Britain and Ireland*. 2016;18(4):357–363.
- Ahmed S, Shahid RK, Leis A, et al. Should non-curative resection of the primary tumour be performed in patients with stage iv colorectal cancer? A systematic review and meta-analysis. *Current oncology (Toronto, Ont.)*. 2013;20(5):e420–441.
- Soreide K, Soreide AH. Using patient-reported outcome measures for improved decision-making in patients with gastrointestinal cancer - the last clinical frontier in surgical oncology? *Frontiers in oncology*. 2013;3:157.
- Cirocchi R, Trastulli S, Abraha I, et al. Non-resection versus resection for an asymptomatic primary tumour in patients with unresectable stage IV colorectal cancer. *The Cochrane database of systematic reviews*. 2012;8:Cd008997.
- Clancy C, Burke JP, Barry M, Kalady MF, Calvin Coffey J. A meta-analysis to determine the effect of primary tumor resection for stage IV colorectal cancer with unresectable metastases on patient survival. *Annals of surgical oncology*. 2014;21(12):3900–3908.
- Gulack BC, Nussbaum DP, Keenan JE, et al. Surgical Resection of the Primary Tumor in Stage IV Colorectal Cancer Without Metastasectomy Is Associated With Improved Overall Survival Compared With Chemotherapy/Radiation Therapy Alone. *Diseases of the colon and rectum*. 2016;59(4):299–305.
- Ishihara S, Hayama T, Yamada H, et al. Prognostic impact of primary tumor resection and lymph node dissection in stage IV colorectal cancer with unresectable metastasis: a propensity score analysis in a multicenter retrospective study. *Annals of surgical oncology*. 2014;21(9):2949–2955.
- Karoui M, Roudot-Thoraval F, Mesli F, et al. Primary colectomy in patients with stage IV colon cancer and unresectable distant metastases improves overall survival: results of a multicentric study. *Diseases of the colon and rectum*. 2011;54(8):930–938.
- Yun JA, Huh JW, Park YA, et al. The role of palliative resection for asymptomatic primary tumor in patients with unresectable stage IV colorectal cancer. *Diseases of the colon and rectum*. 2014;57(9):1049–1058.
- Ishihara S, Nishikawa T, Tanaka T, et al. Benefit of primary tumor resection in stage IV colorectal cancer with unresectable metastasis: a multicenter retrospective study using a propensity score analysis. *International journal of colorectal disease*. 2015;30(6):807–812.
- Ishihara S, Nishikawa T, Tanaka T, et al. Prognostic impact of tumor location in stage IV colon cancer: a propensity score analysis in a multicenter study. *International journal of surgery (London, England)*. 2014;12(9):925–930.
- Rahbari NN, Lordick F, Fink C, et al. Resection of the primary tumour versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases (UICC stage IV): SYNCHRONOUS—a randomised controlled multicentre trial (ISRCTN30964555). *BMC cancer*. 2012;12:142.
- t Lam-Boer J, Mol L, Verhoef C, et al. The CAIRO4 study: the role of surgery of the primary tumour with few or absent symptoms in patients with synchronous unresectable metastases of colorectal cancer—a randomized phase III study of the Dutch Colorectal Cancer Group (DCCG). *BMC cancer*. 2014;14:741.
- Kim CW, Baek JH, Choi GS, et al. The role of primary tumor resection in colorectal cancer patients with asymptomatic, synchronous unresectable metastasis: Study protocol for a randomized controlled trial. *Trials*. 2016;17:34.
- Chen G. Palliative Resection of Asymptomatic Primary Tumor Following Effective Induction Chemotherapy in Colorectal Cancer Patients With Unresectable Distant Metastasis: a Multicenter, Prospective, Randomized Controlled Study. 2014; <https://clinicaltrials.gov/ct2/show/study/NCT02149784?term=NCT02149784&rank=1>. Accessed 20.5.2016, 2016.