Timing of Metastatic Colorectal Cancer

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Contributor: Khawla S Al-Kuraya

Colorectal cancer (CRC) is the third most frequently diagnosed cancer worldwide, where ~50% of patients develop metastasis, despite current improved management. Genomic characterisation of metastatic CRC, and elucidating the effects of therapy on the metastatic process, are essential to help guide precision medicine. Multi-region whole-exome sequencing was performed on 191 sampled tumour regions of patient-matched therapy-naïve and treated CRC primary tumours (n = 92 tumour regions) and metastases (n = 99 tumour regions), in 30 patients. Somatic variants were analysed to define the origin, composition, and timing of seeding in the metastatic progression of therapy-naïve and treated metastatic CRC. High concordance, with few genomic differences, was observed between primary CRC and metastases. Most cases supported a late dissemination model, via either monoclonal or polyclonal seeding. Polyclonal seeding appeared more common in therapy-naïve metastases than in treated metastases. Whereby, treatment prompted for the selection of distinct resistant clones, through monoclonal seeding to distant metastatic sites. Overall, this study reinforces the importance of early clinical detection and surgical excision of the CRC tumour, whilst further highlighting the clinical challenges for metastatic CRC with increased intratumour heterogeneity (either due to early dissemination or polyclonal metastatic spread) and the underlying risk of future therapeutic resistance in treated patients.

Keywords: clonal evolution ; colorectal cancer ; metastasis ; tumour heterogeneity ; clonal spread ; timing ; treatment

1. Background

Colorectal cancer (CRC) is the third most diagnosed cancer worldwide, and one of the top most in Saudi Arabia, with a distinctly earlier (≤10 years) disease onset compared to other ethnicities[1]. High mortality in CRC has been attributed to metastatic disease [1][2][3], whereby half of all patients develop metastasis, despite the improved management of metastatic CRC in recent years[4].

The evolutionary process of CRC is well documented. Whereby, a gradual multi-step model has been used to describe the transformation of intestinal epithelium into invasive adenocarcinoma, from which disseminating tumour cells can then migrate directly, or via haematogenous or lymphogenous spread and colonise regional or distant organs[5], such as the liver, lung, and peritoneum and less frequently the bone and brain[6].

Predominantly, seeding originates from the primary tumour and is spread via a single clone (monoclonal seeding)[7] or multiple subclones (either synchronous or asynchronous polyclonal seeding) to a metastatic site[8][9][10]. Recent studies have also shown metastatic cross-seeding, where one metastasis can seed secondary metastatic sites, via metastatic cascading[11].

Several studies have traditionally defined the process of CRC metastasis through a linear progression or late dissemination model, where metastatic divergence occurs late in the primary tumour relative to tumorigenesis[11][12][13][14]. However, few recent studies have challenged this model, suggesting that metastatic seeding might occur early[15,16], before clinical detectability (<0.01 cm^3) and years before diagnosis or surgery, proposing most CRCs may be “born to be bad”[15].

Understanding the complexity of the metastatic process has been very problematic, even in this advanced genomic era, with difficulties going beyond the procurement of patient-matched paired primary tumours and their distant metastases. Hence, it is of high clinical importance to clarify the origin, seeding composition, and timing of spread to help extricate the evolutionary metastatic process in CRC.

We sought to expand upon current knowledge on the metastatic process in CRC, in the Saudi population, and further highlight the effect of therapy. We used whole-exome sequencing (WES) analysis from multiple tumour regions of paired primary CRC and distant metastatic lesions, from 30 patients with metastatic CRC, to define the origin, composition, and timing of seeding in the metastatic progression of therapy-naïve and treated metastatic CRC tumours.

Overall, this entry reinforces the importance of early detection and removal of the CRC tumour, whilst further highlighting the clinical challenges for metastatic CRC with increased intratumour heterogeneity (either due to early dissemination or polyclonal metastatic spread) and the underlying risk of future therapeutic resistance in treated patients.

2. Brief Results and Discussion

Through systematic analysis of WES data from multiple spatial regions of 30 paired primary CRC and distant metastatic tumours, we describe the overall genomic concordance between primary CRC and metastasis , with predominantly late metastatic divergence, through monoclonal or polyclonal spread from metastatic ‘fit’ clones in the primary tumour. Treatment had a diminutive effect on chromosomal instability and most driver mutations, assumingly to attain resistance mechanisms for increased chances of tumour cell survival . Furthermore, the few existing metastatic-specific driver mutations were mostly found in treated cases, similar to previous studies[16][17][18]. The intratumour heterogeneity, post-dissemination, in treated metastases was likely resultant of the collective dysregulation of DNA repair processes, from defective DNA MMR and HR, and the capecitabine and 5-FU chemotherapy, comparable to recent studies[19].

Of great clinical importance, most cases in our metastatic CRC cohort supported late dissemination, in accordance with the Fearon–Vogelstein multistage progression MSS CRC model[11][12][13][14]. This was consistent, irrespective of treatment status and the organ site colonised. Thus, further highlighting the clinical relevance of current routine screening, and the ability of sigmoid scoping and colonoscopy to successfully detect early CRC lesions, to aid the prevention of metastatic disease. Despite all metastatic-specific driver mutations being present in late disseminating metastases, most driver events were shared between the primary tumour and metastasis, underlining the prospect of using a single diagnostic biopsy from the primary tumour to represent the majority of genomic variation at the metastatic site.

The few metastatic cases in the cohort following an early dissemination model (and similarly cases that incurred polyclonal seeding of the metastasis) can make it difficult to design effective therapeutic strategies using a single biopsy or limited regions, thus warranting the use of additional clinical intervention, such as liquid biopsies (including circulating cell-free tumour DNA profiling) for early detection and metastasis prevention[20]. However, these exceptional cases must not overshadow the importance of screening methods for early detection and the excision of the primary tumour, as suitable ways to reduce CRC mortality in most cases. Two studies have argued that although cancer evolution can be traced using phylogenetic approaches, the timing of dissemination cannot be fully resolved without the aid of other factors, such as chronological references and tumour size or volume, whereby they proposed very early dissemination of primary CRC tumours, i.e., parallel metastatic progression[15,16]. Therefore, metastatic progression in our CRC cohort may also have disseminated earlier than indicated using phylogenetic divergence.

Similar to our metastatic cohort, recent studies have also demonstrated both monoclonal and polyclonal seeding[21]. As expected [22], polyclonal seeding was more common in lymph node metastases (irrespective of treatment) and therapy-naïve distant metastases (55.6%) compared to treated distant metastases (20%). Thus, in the absence of therapy, multiple primary tumour disseminating subclones acquired metastatic potential for seeding regional and distant sites. Polyclonal seeding occurred both synchronously (at the same time) and asynchronously (over multiple waves), arising from distinct spatial regions in the primary tumour. All lymph node metastases that were seeded through polyclonal spread incurred consecutive waves of seeding, possibly due to their geographical proximity to the primary tumour and higher seeding frequency (as the draining lymph nodes encounter higher rates of tumour cells) compared to distant organ sites[23]. Nascent micrometastases may attract subsequent waves of recurrent seeding for the successful colonisation of a distinct metastatic site[24]. Therefore, the removal of primary tumour (or metastasis) after detection in some cases may be clinically necessary to prevent further metastatic seeding. This intervention has particularly been successful in the management of synchronous metastatic disease, whereby excision of the primary tumour with subsequent adjuvant therapy was associated with better overall survival in prostate cancer and non-small cell lung cancer[25][26].

Furthermore, although adjuvant therapy may effectively target micrometastases, preventing (or at least delaying) further metastatic progression for many patients, it selects for resistant subclones that can make subsequent management and treatment more challenging for patients that do inevitably develop metastasis.

This study was mostly (>70% of primary CRC and distant metastases) based on multi-region WES of precious patient-matched primary CRC and metastatic tumour samples, with additional lymph node metastases in three cases. Furthermore, ultra-depth targeted sequencing (median 2691×, range 1921–3842) was used to validate all somatic variants. Collectively, this allowed a higher resolution for the detection of subclonal mutations, more accurate phylogenetic analysis, and identification of polyclonal seeding patterns. However, the results of this study need to be validated in a larger cohort of multi-region patient-matched primary and metastatic high-depth sequenced data.

3. Conclusion

This entry provides valuable insight into our understanding of tumour evolution and the effect of therapy on metastatic CRC, especially in the Saudi population, with recognised earlier disease onset. Despite most of our cases supporting a late dissemination model, the presence of cases that either incurred prior treatment or have additional intratumour heterogeneity (due to early dissemination or polyclonal spread to the metastasis) may raise clinical challenges for targeted therapy and metastasis prevention. However, the results of this study need to be validated in a larger cohort.

References

1. Bazarbashi, S. Cancer Incidence Report Saudi Arabia 2014. Available online at: https://nhic.gov.sa/eServices/Documents/2014.pdf (accessed on 14th April 2020)
2. Siegel, R.; Miller, K.D.; Sauer, A.G.; Fedewa, S.A.; Butterly, L.F.; Anderson, J.C.; Cercek, A.; Smith, R.A.; Jemal, A. Colorectal cancer statistics, 2020. CA: A Cancer J. Clin. 2020, 70, 145–164, doi:10.3322/caac.21601.
3. Ghiringhelli, F.; Hennequin, A.; Drouillard, A.; Lepage, C.; Faivre, J.; Bouvier, A.-M. Epidemiology and prognosis of synchronous and metachronous colon cancer metastases: A French population-based study. Dig. Liver Dis. 2014, 46, 854–858, doi:10.1016/j.dld.2014.05.011.
4. Van Cutsem, E.; Cervantes, A.; Nordlinger, B.; Arnold, D. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 2014, 25, iii1–iii9, doi:10.1093/annonc/mdu260.
5. Vogelstein, B.; Fearon, E.R.; Hamilton, S.R.; Kern, S.E.; Preisinger, A.C.; Leppert, M.; Smits, A.M.; Bos, J.L. Genetic Alterations during Colorectal-Tumor Development. New Engl. J. Med. 1988, 319, 525–532, doi:10.1056/nejm198809013190901.
6. Turajlic, S.; Swanton, C. Metastasis as an evolutionary process. Science 2016, 352, 169–175, doi:10.1126/science.aaf2784.
7. Huang, Y.; Gao, S.; Wu, S.; Song, P.; Sun, X.; Hu, X.; Zhang, S.; Yu, Y.; Zhu, J.; Li, C.; et al. Multilayered molecular profiling supported the monoclonal origin of metastatic renal cell carcinoma. Int. J. Cancer 2013, 135, 78–87, doi:10.1002/ijc.28654.
8. MacIntyre, G.; Van Loo, P.; Corcoran, N.M.; Wedge, D.C.; Markowetz, F.; Hovens, C.M. How Subclonal Modeling Is Changing the Metastatic Paradigm. Clin. Cancer Res. 2016, 23, 630–635, doi:10.1158/1078-0432.ccr-16-0234.
9. Heyde, A.; Reiter, J.G.; Naxerova, K.; Nowak, M.A. Consecutive seeding and transfer of genetic diversity in metastasis. Proc. Natl. Acad. Sci. USA 2019, 116, 14129–14137, doi:10.1073/pnas.1819408116.
10. Ulintz, P.J.; Greenson, J.K.; Hardiman, K.M.; Wu, R.; Fearon, E.R. Lymph Node Metastases in Colon Cancer Are Polyclonal. Clin. Cancer Res. 2017, 24, 2214–2224, doi:10.1158/1078-0432.ccr-17-1425.
11. Dang, H.X.; Krasnick, B.; White, B.S.; Grossman, J.G.; Strand, M.S.; Zhang, J.; Cabanski, C.R.; Miller, C.A.; Fulton, R.S.; Goedegebuure, S.P.; et al. The clonal evolution of metastatic colorectal cancer. Sci. Adv. 2020, 6, eaay9691, doi:10.1126/sciadv.aay9691.
12. Leung, M.L.; Davis, A.; Gao, R.; Casasent, A.; Wang, Y.; Sei, E.; Vilar, E.; Maru, D.; Kopetz, S.; E.; Navin, N. Single-cell DNA sequencing reveals a late-dissemination model in metastatic colorectal cancer. Genome Res. 2017, 27, 1287–1299, doi:10.1101/gr.209973.116.
13. Fearon, E.R.; Vogelstein, B. A genetic model for colorectal tumorigenesis. Cell 1990, 61, 759–767, doi:10.1016/0092-8674(90)90186-i.
14. Ishaque, N.; Abba, M.L.; Hauser, C.; Patil, N.; Paramasivam, N.; Huebschmann, D.; Leupold, J.H.; Balasubramanian, G.P.; Kleinheinz, K.; Toprak, U.H.; et al. Whole genome sequencing puts forward hypotheses on metastasis evolution and therapy in colorectal cancer. Nat. Commun. 2018, 9, 4782, doi:10.1038/s41467-018-07041-z.
15. Hu, Z.; Ding, J.; Ma, Z.; Sun, R.; Seoane, J.A.; Shaffer, J.S.; Suarez, C.J.; Berghoff, A.S.; Cremolini, C.; Falcone, A.; et al. Quantitative evidence for early metastatic seeding in colorectal cancer. Nat. Genet. 2019, 51, 1113–1122, doi:10.1038/s41588-019-0423-x.
16. Priestley, P.; Baber, J.; Lolkema, M.P.; Steeghs, N.; De Bruijn, E.; Shale, C.; Duyvesteyn, K.; Haidari, S.; Van Hoeck, A.; Onstenk, W.; et al. Pan-cancer whole-genome analyses of metastatic solid tumours. Nat. Cell Biol. 2019, 575, 210–216, doi:10.1038/s41586-019-1689-y.
17. Yaeger, R.; Chatila, W.K.; Lipsyc, M.D.; Hechtman, J.F.; Cercek, A.; Sanchez-Vega, F.; Jayakumaran, G.; Middha, S.; Zehir, A.; Donoghue, M.T.; et al. Clinical Sequencing Defines the Genomic Landscape of Metastatic Colorectal Cancer. Cancer Cell 2018, 33, 125–136.e3, doi:10.1016/j.ccell.2017.12.004.

18. Zehir, A.; Benayed, R.; Shah, R.H.; Syed, A.; Middha, S.; Kim, H.R.; Srinivasan, P.; Gao, J.; Chakravarty, D.; Devlin, S.M.; et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat. Med. 2017, 23, 703–713, doi:10.1038/nm.4333.

19. Sun, J.; Wang, C.; Zhang, Y.; Xu, L.; Fang, W.; Zhu, Y.; Zheng, Y.; Chen, X.; Xie, X.; Hu, X.; et al. Genomic signatures reveal DNA damage response deficiency in colorectal cancer brain metastases. Nat. Commun. 2019, 10, 3190, doi:10.1038/s41467-019-10987-3.

20. Yamada, T.; Matsuda, A.; Koizumi, M.; Shinji, S.; Takahashi, G.; Iwai, T.; Takeda, K.; Ueda, K.; Yokoyama, Y.; Hara, K.; et al. Liquid Biopsy for the Management of Patients with Colorectal Cancer. Digestion 2018, 99, 39–45, doi:10.1159/000494411.

21. Hu, Z.; Li, Z.; Ma, Z.; Curtis, C. Multi-cancer analysis of clonality and the timing of systemic spread in paired primary tumors and metastases. Nat. Genet. 2020, 52, 1–8, doi:10.1038/s41588-020-0628-z.

22. Wei, Q.; Ye, Z.; Zhong, X.; Li, L.; Wang, C.; Myers, R.E.; Palazzo, J.P.; Fortuna, D.; Yan, A.; Waldman, S.A.; et al. Multiregion whole-exome sequencing of matched primary and metastatic tumors revealed genomic heterogeneity and suggested polyclonal seeding in colorectal cancer metastasis. Ann. Oncol. 2017, 28, 2135–2141, doi:10.1093/annonc/mdx278.

23. Reiter, J.G.; Hung, W.-T.; Lee, I.-H.; Nagpal, S.; Giunta, P.; Degner, S.; Liu, G.; Wassenaar, E.C.E.; Jeck, W.R.; Taylor, M.S.; et al. Lymph node metastases develop through a wider evolutionary bottleneck than distant metastases. Nat. Genet. 2020, 52, 692–700, doi:10.1038/s41588-020-0633-2.

24. Gundem, G.; Van Loo, P.; Kremeyer, B.; Alexandrov, L.B.; Tubio, J.M.C.; Papaemmanuil, E.; Brewer, D.S.; Kallio, H.M.; Högnäs, G.; Annala, M; et al. The evolutionary history of lethal metastatic prostate cancer. Nat. Cell Biol. 2015, 520, 353–357, doi:10.1038/nature14347.

25. Löppenberg, B.; Dalela, D.; Karabon, P.; Sood, A.; Sammon, J.D.; Meyer, C.P.; Sun, M.; Noldus, J.; Peabody, J.O.; Trinh, Q.-D.; et al. The Impact of Local Treatment on Overall Survival in Patients with Metastatic Prostate Cancer on Diagnosis: A National Cancer Data Base Analysis. Eur. Urol. 2017, 72, 14–19, doi:10.1016/j.eururo.2016.04.031.

26. Fleckenstein, J.; Petroff, A.; Schäfers, H.-J.; Wehler, T.; Schöpe, J.; Rübe, C. Long-term outcomes in radically treated synchronous vs. metachronous oligometastatic non-small-cell lung cancer. BMC Cancer 2016, 16, 348, doi:10.1186/s12885-016-2379-x.

27. Siraj, A.K.; Masoodi, T.; Bu, R.; Pratheeshkumar, P.; Al-Sanea, N.; Ashari, L.H.; Abduljabbar, A.; Alhomoud, S.; Al-Dayel, F.; Alkuraya, F.S.; et al. MED12is recurrently mutated in Middle Eastern colorectal cancer. Gut 2017, 67, 663–671, doi:10.1136/gutjnl-2016-313334.

28. Abubaker, J.; Bavi, P.; Al-Harbi, S.; Ibrahim, M.; Siraj, A.K.; Alsanea, N.; Abduljabbar, A.; Ashari, L.H.; Alhomoud, S.; Al-Dayel, F.; et al. Clinicopathological analysis of colorectal cancers with PIK3CA mutations in Middle Eastern population. Oncogene 2008, 27, 3539–3545, doi:10.1038/sj.onc.1211013.

29. Liu, Z.; Yang, C.; Li, X.; Luo, W.; Roy, B.; Xiong, T.; Zhang, X.; Yang, H.; Wang, J.; Ye, Z.; et al. The landscape of somatic mutation in sporadic Chinese colorectal cancer. Oncotarget 2018, 9, 27412–27422, doi:10.18632/oncotarget.25287.

30. Uchi, R.; Takahashi, Y.; Niida, A.; Shimamura, T.; Hirata, H.; Sugimachi, K.; Sawada, G.; Iwaya, T.; Kurashige, J.; Shinden, Y., Integrated multiregional analysis proposing a new model of colorectal cancer evolution. PLoS Genetics 2016, 12, e1005778.

31. McGranahan, N.; Favero, F.; De Bruin, E.C.; Birkbak, N.J.; Szallasi, Z.; Swanton, C. Clonal status of actionable driver events and the timing of mutational processes in cancer evolution. Sci. Transl. Med. 2015, 7, 283ra54, doi:10.1126/scitranslmed.aaa1408.

32. Hu, Z.; Li, Z.; Ma, Z.; Curtis, C. Multi-cancer analysis of clonality and the timing of systemic spread in paired primary tumors and metastases. Nat. Genet. 2020, 52, 1–8, doi:10.1038/s41588-020-0628-z.

33. Reiter, J.G.; Hung, W.-T.; Lee, I.-H.; Nagpal, S.; Giunta, P.; Degner, S.; Liu, G.; Wassenaar, E.C.E.; Jeck, W.R.; Taylor, M.S.; et al. Lymph node metastases develop through a wider evolutionary bottleneck than distant metastases. Nat. Genet. 2020, 52, 692–700, doi:10.1038/s41588-020-0633-2.

34. Priestley, P.; Baber, J.; Lolkema, M.P.; Steeghs, N.; De Bruijn, E.; Shale, C.; Duyvesteyn, K.; Haidari, S.; Van Hoeck, A.; Onstenk, W.; et al. Pan-cancer whole-genome analyses of metastatic solid tumours. Nat. Cell Biol. 2019, 575, 210–216, doi:10.1038/s41586-019-1689-y.

35. Yaeger, R.; Chatila, W.K.; Lipsyc, M.D.; Hechtman, J.F.; Cercek, A.; Sanchez-Vega, F.; Jayakumaran, G.; Middha, S.; Zehir, A.; Donoghue, M.T.; et al. Clinical Sequencing Defines the Genomic Landscape of Metastatic Colorectal Cancer. Cancer Cell 2018, 33, 125–136.e3, doi:10.1016/j.ccell.2017.12.004.

36. Zehir, A.; Benayed, R.; Shah, R.H.; Syed, A.; Middha, S.; Kim, H.R.; Srinivasan, P.; Gao, J.; Chakravarty, D.; Devlin, S.M.; et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat. Med. 2017, 23, 703–713, doi:10.1038/nm.4333.
37. Sun, J.; Wang, C.; Zhang, Y.; Xu, L.; Fang, W.; Zhu, Y.; Zheng, Y.; Chen, X.; Xie, X.; Hu, X.; et al. Genomic signatures reveal DNA damage response deficiency in colorectal cancer brain metastases. Nat. Commun. 2019, 10, 3190, doi:10.1038/s41467-019-10987-3.
38. Yamada, T.; Matsuda, A.; Koizumi, M.; Shinji, S.; Takahashi, G.; Iwai, T.; Takeda, K.; Ueda, K.; Yokoyama, Y.; Hara, K.; et al. Liquid Biopsy for the Management of Patients with Colorectal Cancer. Digestion 2018, 99, 39–45, doi:10.1159/000494411.
39. Wei, Q.; Ye, Z.; Zhong, X.; Li, L.; Wang, C.; Myers, R.E.; Palazzo, J.P.; Fortuna, D.; Yan, A.; Waldman, S.A.; et al. Multiregion whole-exome sequencing of matched primary and metastatic tumors revealed genomic heterogeneity and suggested polyclonal seeding in colorectal cancer metastasis. Ann. Oncol. 2017, 28, 2135–2141, doi:10.1093/annonc/mdx278.
40. Gundem, G.; Van Loo, P.; Kremeyer, B.; Alexandrov, L.B.; Tubio, J.M.C.; Papaemmanuil, E.; Brewer, D.S.; Kallio, H.M.; Högnäs, G.; Annala, M; et al. The evolutionary history of lethal metastatic prostate cancer. Nat. Cell Biol. 2015, 520, 353–357, doi:10.1038/nature14347.
41. Löppenberg, B.; Dalela, D.; Karabon, P.; Sood, A.; Sammon, J.D.; Meyer, C.P.; Sun, M.; Noldus, J.; Peabody, J.O.; Trinh, Q.-D.; et al. The Impact of Local Treatment on Overall Survival in Patients with Metastatic Prostate Cancer on Diagnosis: A National Cancer Data Base Analysis. Eur. Urol. 2017, 72, 14–19, doi:10.1016/j.eururo.2016.04.031.
42. Fleckenstein, J.; Petroff, A.; Schäfers, H.-J.; Wehler, T.; Schöpe, J.; Rübe, C. Long-term outcomes in radically treated synchronous vs. metachronous oligometastatic non-small-cell lung cancer. BMC Cancer 2016, 16, 348, doi:10.1186/s12885-016-2379-x.