Tree interpretation

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1. M055: In patient M055, the phylogenetic tree can be interpreted in two ways: PT seed both PM1 and PM2; one PM seed the other. But because both PM1 and PM2 were diagnosed at the same time with similar tumor sizes, it is more likely that the PT seeded both PMs (We expect that precursor MT and subsequent reseeded MTs either have a lag in time or a significant difference in tumor size).
2. M114: For patient M114, the phylogenetic tree can be interpreted in two ways: (1) PM and SpM metastasis were seeded by early metastasis from PT; (2) PM reseeded SpM and then SpM reseed PT region being sampled. Considering (a) Reseeding from MT is considered to be very rare based on existing literatures. (b) Model 1 predicted SpM is a polyclonal metastasis, which is consistent with short survival time for this patients. (c) PM and SpM were detected at the same time. We think the model 1, where PT seeded all MTs are more likely than MT reseeding PT model 2.
3. M168: The patient M168 is a complex case. The LM1\_2/LNM cluster can be interpreted in two ways: PT seed LM1\_2 and LNM respectively, or one seed the other(LM1\_2 to LNM). LNM was diagnosed only about four months later from the detection of LM1\_2. Similarly, the LM1\_1/LM2\_3 cluster can be interpreted in two ways: PT seed LM1\_1 and LM2\_3 respectively, or one seed the other(LM1\_1 to LM2\_3 or in reverse order). Both LM1 and LM2 were detected at the same time with similar tumor size. Therefore for LM1\_2, LNM, LM1\_1 and LM2\_3, we considered the MT seeded MT pattern is less likely compared than PT seeded MT pattern. However, we did admit that we couldn’t completely rule out the possibility that MT reseed MT in M055, M114 and M168. But based on our assessment on multiple layers of evidence both in term of genetics and clinical information we tried to derive the most likely interpretation for the tumor evolutionary trajectories.
4. MT seed MT example: M028 and M048: Both MT seeded MT examples (M048 and M028) were shown in the main Figure 2C and 2D, in both of these cases there is a time lag between the initial MTs and subsequent MTs. In M048, the multiple-regional sampled PTs and LM tumors give us more confidence that LM were reseeded from DM, but not PTs. In addition, the time gap between seeding MT (DM) and subsequent MTs (LM1/2) in M048 is more than two years. In M028, multiple regional sampled AGM1 also gave us strong evidence that AGM2 was seeded from AGM1\_3 region. In addition, the time gap between seeding MT (AGM1) and subsequent MT (AGM2) in M028 is more than one year. We plan to add few sentences in the supplementary figure legend and online supplementary materials in Github (https://github.com/bioliyezhang/HCC\_Metastasis) to describe these complex cases like M055, M114 and M168, and explain why we categorized them into PT seeded MT, but not MT seeded MT. But we did agree that the trees didn’t fully exclude the possibility of MT reseeding.