1	SUPPLEMENTARY INFORMATION
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4	Rapid evolution and biogeographic spread in a colorectal
5	cancer
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18 Supplementary Note 1. Spatial distribution of bulk tumor samples

19 To assess whether the biogeographical solution described in the main text was robust to 20 changes in the geographical coordinates assigned to each tumor sample, we generated five 2D 21 spatial matrices corresponding to alternative migration distances among the tumor samples 22 (Supplementary fig. 4). Remarkably, three out of the five 2D matrices resulted in the same 23 migration history as the one described in the main text. Interestingly, for matrix 3, in which the 24 geographical locations of both colonic and hepatic lymph nodes were spaced far apart from the colon and liver, BayArea¹ inferred a biogeographic solution where the ancestral metastatic 25 26 clone was located in hepatic lymph nodes. In addition, for matrix 5, in which the spatial 27 distance between all organs was substantially reduced, BayArea inferred a migratory dissemination very similar to the one presented in the main text, but suggesting an earlier 28 29 movement of metastatic clones in the liver to nearby hepatic lymph nodes.

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31 Supplementary Note 2. Inferring migration history at the sample level using MACHINA

We additionally ran MACHINA² at the sample level, under parsimonious migration history mode, 32 by setting each sampled location as a different anatomical site. Since eight primary tumor 33 34 locations were sampled, all of them were tested in turn as potential primary anatomical sites. 35 This resulted in a total of 30,924 migration histories. Focusing solely at the inferred histories 36 where the primary anatomical site was assumed to be C3 (i.e., the primary anatomical site 37 inferred using BayArea), 18 maximum parsimony histories (MP) were inferred. One of the 18 38 inferred MP histories is fairly similar to the biogeographic history reconstructed with BayArea, although it suggests an early metastatic dissemination followed by a subsequent migration back 39 40 to the primary tumor (L1 -> C1). Altogether, these MACHINA results seem rather inconclusive. 41





43 Supplementary Figure 1. Overall and tissue-specific correlation between geographic distance

44 and genetic distance. The geographic distance matrix consists of pairwise comparisons of the

45 spatial location of tumor samples in *Matrix 1*. The genetic distance matrix consists of pairwise

46 *Fst* estimates³. A Mantel test⁴ was performed in R comparing the two distance matrices using

47 1000 replicates.



50 **Supplementary Figure 2. Uncertainty of the phylogenetic dating with *BEAST.** Lower and 51 upper 95% HPD age estimates in years obtained from *BEAST are shown for tree nodes with 52 posterior support > 0.5. Nodes with posterior probability values > 0.9 and > 0.5 are highlighted

53 with black and grey solid circles, respectively. Clone IDs are shown at the tips of the tree.



56 **Supplementary Figure 3. Phylogenetic reconstruction obtained with CloneFinder and LICHEE.**

57 Maximum likelihood trees obtained using heuristic search in PAUP*⁵. Clonal IDs are shown at

58 the tips of the phylogenetic trees (A-U for CloneFinder; A-R for LICHeE). Colored rectangles

59 highlight the anatomical location of each clone: Green - Primary tumor, Yellow - Metastases.



63 Supplementary Figure 4. Spatial organization of bulk tumor samples and biogeographic reconstruction. (Top) 2D coordinate matrices depicting alternative migration tumor samples. 64 65 Solid circles represent each sample. Colors highlight the anatomical location of each sample: 66 Colon - Green; Colonic Lymph Nodes - Gold; Hepatic Lymph Nodes - Salmon; Liver - Red. 67 (Bottom) Biogeographic reconstruction resulting from BayArea using the corresponding 2-D 68 matrix. At two key nodes (tMRCA and mMRCA), the highest posterior probability area range is 69 depicted. Sample IDs are shown at internal nodes. The locations where the extant clones were 70 sampled are shown next to the tips. 71





73 Supplementary Figure 5. Parsimonious migration inference with MACHINA. Migration graphs

inferred under *phm_sankoff* mode and setting the colon as the primary tumor location.
 Migratory solutions ordered based on the number of inferred migrations and comigrations.

76 Solution 1 is the most parsimonious because it implies the smallest number of events. For each

77 graph, colored squares depict the anatomical sites sampled: Colon - red, CL - blue, HL - green,

- 78 Liver purple. Arrows indicate clonal movements.
- 79





Supplementary Figure 6. Representative FACS gate strategy showing the frequency of EpCAM+ cells in sample C8. We used the scatter gate to remove cell debris, then we gated the nucleated cells and select alive ones base on DRAQ5 and 7AAD signals. After that we removed aggregates. Finally we gated EpCAM+DRAQ5+7AAD- cells and sorted this population.

Supplementary Table 1. Evolutionary models tested in BEAST.

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104 Supplementary References

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