2239

Detecting Cancer When It Can Be Cured: The Potential For Cure Across All Stageable Cancers

Annual Meeting of the American Association for Cancer Research.
April 8 – 13, 2022.
New Orleans, Louisiana

Earl Hubbell and Christina A. Clarke
GRAIL, LLC, a subsidiary of Illumina, Inc., Menlo Park, CA.

INTRODUCTION

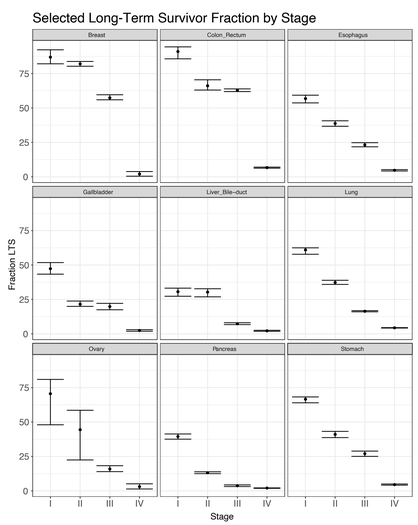
- Cancer is a leading cause of death in the United States[1]
- Due to limited cancer screening options,[2] many cancers, such as pancreas, gallbladder, and esophagus, are discovered only at late stages when outcomes are worse
- Deaths due to cancer are overwhelmingly associated with detection of disease at later stages, when a cure is less likely[3]
- Cancer cure does not have a simple, universally agreed upon definition and the best way to model individual and population-level "cure" outcomes is still debated[4]
- One such model, known as a mixture cure model, divides cancer patients into two populations:[5]
  - Proportion not cured: cancer is likely to severely impact mortality
  - Proportion cured: long-term survival with low cancer-specific mortality risk is possible
- Previous work on such mixture cure models has either
  - Estimated the fraction of population cured for many cancer types without regard to stage for public health purposes,[5–9] or
  - Estimated for single cancer types the fraction of population cured by stage for screenable cancers[10]
- The current literature lacks a description of the spectrum of the fraction of the population cured across all different cancer types at all stages of diagnosis
- To quantify the mortality differences between early and late stage disease, we estimate the proportion of effectively cured individuals by stage across many cancer types

OBJECTIVE

- Determine the fraction of the population that could potentially be cured for the full spectrum of cancer types at each stage

KEY RESULTS: SUBSTANTIAL FRACTIONS OF LONG-TERM SURVIVORS ARE FOUND AT EARLY STAGES ACROSS ALL CANCER TYPES EXAMINED

Figure 1. Nine Illustrative Cancer Types



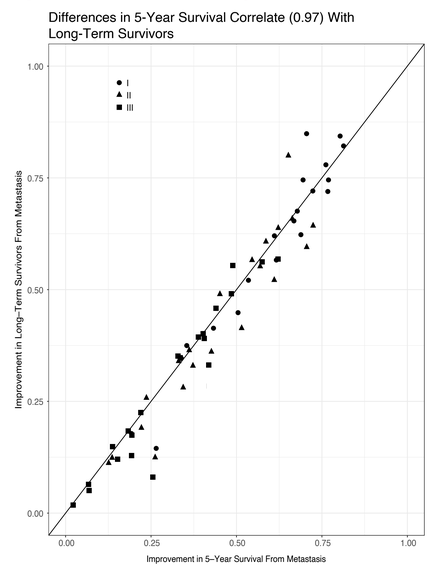
The fraction of long-term cancer-specific survival (LTS, y-axis) with error bars for each stage (x-axis) of nine selected cancers. SEER data for 50-79 year olds. Note that even in the not-cured fraction individuals may survive many years dependent on the parameters of the Weibull. Some uncertainty in LTS fraction occurs at cancer types and stages where hazard is very low and does not rule out a large number of extrapolated survivors at 25 years or more. This indicates uncertainty in assigning such survivors to one of the two populations.

Table 1: Fitted Cure Fraction and Excess Risk of Cancer-Specific Death by Stage for 21 Cancer Types

Cancer Type	Stage I		Stage II		Stage III		Stage IV	
	Cure Fraction[a] (95% CI)	Excess Annual Risk[b]	Cure Fraction[a] (95% CI)	Excess Annual Risk[b]	Cure Fraction[a] (95% CI)	Excess Annual Risk[b]	Cure Fraction[a] (95% CI)	Excess Annual Risk[b]
Anus	88 (81-95)	0.5	83 (78-86)	0.8	69 (65-71)	0.9	23 (19-26)	1.1
Bladder	92 (88-93)	1.5	66 (65-67)	1.7	52 (50-54)	1.7	17 (16-18)	1.8
Breast	87 (82-92)	0	82 (80-84)	0.1	57 (56-60)	0.2	2 (0-4)	1.1
Cervix	91 (86-93)	0.5	75 (71-79)	1.4	54 (51-56)	1.7	19 (17-21)	1.9
Colorectal	91 (86-94)	0.8	66 (63-70)	0.8	63 (62-64)	0.8	7 (6-7)	0.9
Esophagus	57 (54-59)	1.2	39 (37-41)	1.8	23 (22-25)	1.9	5 (4-5)	2
Gallbladder	47 (43-52)	0.5	22 (20-24)	1.2	20 (17-22)	1.5	2 (2-3)	1.8
Head/Neck	94 (94-95)	1.4	86 (84-87)	1.9	75 (74-76)	2	60 (59-61)	2
Kidney	93 (84-98)	0.9	76 (64-87)	1.4	68 (57-74)	1.7	11 (10-12)	1.9
Liver	31 (27-33)	0.9	30 (27-33)	1	7 (7-8)	1.8	2 (2-3)	1.9
Lung	61 (58-62)	1.9	37 (36-39)	1.9	16 (16-17)	2	4 (4-5)	2
Lymphoma	90 (90-91)	1.2	85 (84-86)	1.4	79 (78-80)	1.8	72 (72-73)	2
Melanoma	94 (93-94)	0	74 (72-77)	0.2	61 (59-63)	1.3	22 (20-23)	1.4
Ovary	71 (48-81)	0.1	44 (22-59)	0.3	16 (14-18)	0.5	3 (1-5)	1.3
Pancreas	39 (38-41)	1.9	13 (13-14)	1.9	4 (3-4)	1.9	2 (2-2)	2
Prostate	88 (83-95)	0	83 (81-86)	0	80 (76-83)	0	47 (45-48)	1.9
Sarcoma	85 (75-91)	0.6	74 (69-80)	1.1	50 (46-54)	1.6	10 (8-12)	1.8
Stomach	67 (64-68)	1	41 (39-43)	1.8	27 (25-29)	1.9	5 (4-5)	1.9
Thyroid	96 (91-99)	0	94 (87-98)	0.1	90 (82-96)	0.1	82 (81-83)	2
Urothelial Tract	79 (70-88)	0.9	72 (65-78)	1.3	56 (53-60)	1.6	17 (15-19)	1.8
Uterus	94 (93-95)	0.2	82 (80-84)	0.3	65 (63-67)	0.9	16 (15-18)	1.6

[a]Fitted long-term cancer-specific survival fractions. [b]Excess yearly risk in those cured. SEER data for ages 50-79 for 21 listed cancer types.

Figure 2. Standard Metrics and Long-Term Survival



Difference in 5-year cancer-specific survival rates from metastasis for each cancer type and stage I-III are plotted as a predictor of differences in long-term survivor fraction for the same stages.

Two Major Cancer Survival Patterns Were Observed

- Cure fractions varied among cancer types and stages at diagnosis, with most following one of two cancer behavior patterns (**Figure 1** and **Table 1**)
- Examples of these two cancer behavior patterns can be illustrated by colorectal and gallbladder cancers (**Figure 1** and **Table 1**)
  - Colorectal cancer had a good potential for cure at any stage before metastasis, with a precipitous drop from 63% (95% CI: 62-64%) cure at stage III to 7% (6-7%) cure at stage IV
  - In contrast, gallbladder cancer exhibited a systematic decrease at each stage, with 47% (43-52%) cure fraction at stage I, 22% (20-24%) at stage II, 20% (17-22%) at stage III, and 2% (2-3%) at stage IV
- Modeled estimates of cure fraction and the variation by stage at diagnosis for nine selected cancers are shown in **Figure 1**
- Diversity of fitted long-term survivor fractions and the uncertainty associated with each can be seen through the size of associated error bars
  - For example, in colorectal cancer, stage III provides a stronger estimate of the cure fraction than stage II, which is why the lower bounds of the stage II confidence interval is below the upper bound of the stage III confidence interval
- For most cancers, cure fraction was noticeably higher at stage I and II compared to III and IV (**Figure 1** and **Table 1**)
- Adding a small excess risk improves the likelihood of the fit noticeably, and was consistent with other studies of long-term recurrence and relapse

Using 5-Year Survival Differences as a Predictor of Long-Term Cancer-Specific Survival Differences

- Combining the 5-year cancer-specific survival for each early stage and the difference from metastasis to estimate the percentage difference in 5-year survival is a strong predictor of the difference in the long-term survival population (**Figure 2**)
- In general, there are very few long-term survivors at metastasis, even if the 5-year cancer-specific survival is not zero for metastatic cancer case
- The differences in percentage in the starting population of long-term survivors is well predicted by this difference in 5-year cancer-specific survival rates. For example:
  - If 5-year survival is 60% at stage I and 20% at stage IV, there will be about 40% more long-term survivors at stage I than stage IV
  - If stage IV has no long-term survivors, then stage I would be predicted to have about 40% long-term survivors

CONCLUSIONS

- A noticeable fraction of long-term cancer survivors were evident at early stages for each of 21 cancer types examined
- Cancer-specific survival fractions were greatly reduced by the time cancer reached metastasis
- Although 5-year survival is not itself long-term survival, differences in 5-year cancer-specific survival are strong predictors of differences in long-term cancer-specific survival in a cancer type
- The observed differences in long-term survivors suggest that early and late stage cancer survival curves are not due to lead time bias
- This analysis provides statistical evidence in support of the potential for detection of cancer in early stages to result in long-term cancer-specific survival for many stageable cancer types, including ones with no current screening modality

METHODS

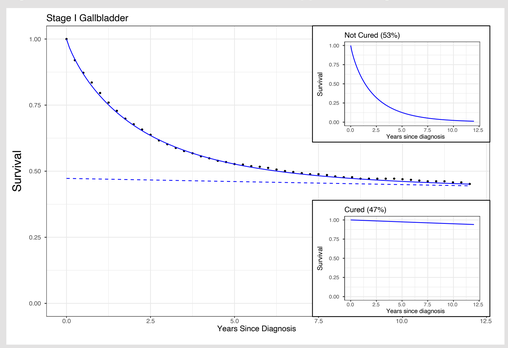
Data Source

- We estimate a mixture-cure model for all stages simultaneously for 21 cancers with standard American Joint Committee on Cancer (AJCC) 6th edition staging and available data in SEER
- We obtained from SEER18 monthly life-tables for cancer-specific survival for patients diagnosed with invasive cancers 50-79 years of age, diagnosed in 2006-2015 with follow-up to 2018.[11] Cancer types were defined by ICD-0-3 site and histology groupings available upon request

Population Survival

- Population survival is modeled as a mixture of two populations
  - The severe mortality subgroup is modeled as having a two-parameter Weibull distribution for survival
  - The long-term survivor subgroup (cured) is modeled as having a small exponential hazard
    - Strict zero-risk cure may not be possible or resolvable from data for some cancers (eg, non-small cell lung),[12] so we allow a small excess hazard in the cured group to account for this possibility[12–14]

Figure 3. Illustration of Mixture-Cure Model Applied to Stage I Gallbladder

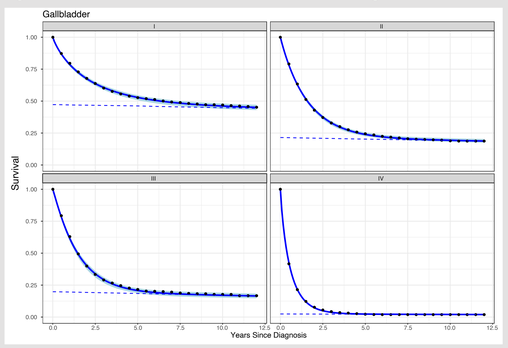


Survival for stage I gallbladder cancer versus years since diagnosis. Dots are direct cancer-specific survival estimates from SEER obtained from the life tables, plotted every 3 months. Solid blue line represents the median fitted survival aggregating both the cured and not cured together. Dashed blue line represents the individuals surviving in the "cured" subset of the population. The inserts show the modeled curves for each of the "not cured" and "cured" populations.

Example Curves - Gallbladder

- We report here the fraction of long-term survivors ("cured" fraction) by stage, as well as the potential excess risk within that group
- Examples of the output of these techniques are shown in **Figures 3** and **4**
- The 53% of individuals in the "not-cured" category follow a Weibull distribution for survival (**Figure 3**)
- The 47% of individuals in the "cured" category follow a long-term cancer-specific survival curve that has a very low hazard of recurrence
- By combining the two curves on each population fraction, a fit of the cancer-specific survival data is accomplished
- The tight fit shown in **Figure 3** is repeated through all gallbladder cancer stages (**Figure 4**)

Figure 4. Simultaneous Fits of the Model Across All 4 Stages for Gallbladder



Dots represent direct cancer-specific survival estimates from SEER obtained from the life tables, plotted every 6 months. Blue line represents the median fitted survival for the whole population, and the blue shadow indicates the 95% confidence interval for the fitted survival. Confidence interval obtained from the sampled parameters of the MCMC fit. Dashed line indicates the trajectory of the long-term survivor population.

Model Parameters

- We use the fact that cancer is a progressive disease as a constraint on model parameters to stabilize fitting across all stages simultaneously
  - The Weibull distribution for the not-cured in each stage is constrained so that long-term mortality is worse by later stage of cancer
  - The exponential hazard for the long-term survivors (cured) is constrained so that later stages have more potential for recurrence
  - The fraction of long-term survivors is constrained to decrease with later stage
- The model is fit using a Markov chain Monte Carlo (MCMC) technique[15] to
  - Optimize the likelihood of data given a parameter set and
  - Recover uncertainty in parameters given the data while respecting the constraints by stage

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. *CA Cancer J Clin.* 2022;72(1):7-33. doi:10.3322/caac.21708
2. United States Preventive Services Task Force. Published 2019. https://www.uspreventiveservicestaskforce.org/Page/Name/uspstf-a-and-b-recommendations/
3. Clarke CA, Hubbell E, Kurian AW, Colditz GA, Hartman AR, Gomez SL. *Cancer Epidemiol Biomarkers Prev.* 2020;29(5):895-902. doi:10.1158/1055-9965.EPI-19-1366
4. Tralongo P, Surbone A, Serrano D, Dal Maso L. *Eur J Cancer Care (Engl).* 2019;28(6):e13139. doi:10.1111/ecc.13139
5. Ovcaricek M, Kagnes B, Fosså SD, Lambert PC, Møller B, Bray F. *Int J Cancer.* 2013;132(7):1700-1710. doi:10.1002/ijc.27802
6. Romain G, Boussari O, Bossard N, et al. *Cancer Epidemiol.* 2019;60:93-101. doi:10.1016/j.canep.2019.02.006
7. Dal Maso L, Guzzinati S, Buzzoni C, et al. *Ann Oncol Off J Eur Soc Med Oncol.* 2014;25(11):2251-2260. doi:10.1093/annonc/mdu383
8. Dal Maso L, Panato C, Guzzinati S, et al. *Cancer Med.* 2019;8(8):4497-4507. doi:10.1002/cam4.2276
9. Dal Maso L, Panato C, Tavilla A, et al. *Int J Epidemiol.* 2020;49(3):1517-1525. doi:10.1093/ije/dyaa128
10. Stedman MR, Feuer EJ, Mariotto AB. *J Natl Cancer Inst Monogr.* 2014;2014(49):244-254. doi:10.1093/jncimonographs/lgu015
11. Surveillance Epidemiology and End Results (SEER) Program. National Cancer Institute; 2020. Accessed September 30, 2021. www.seer.cancer.gov
12. Hubbard MO, Fu P, Margevicius S, Dowlati A, Linden PA. *J Thorac Cardiovasc Surg.* 2012;143(6):1307-1313. doi:10.1016/j.jtcvs.2012.01.078
13. Dood RL, Zhao Y, Armbruster SD, et al. *JAMA Oncol.* 2018;4(11). doi:10.1001/jamaoncol.2018.2761
14. Rueda DM, Samhuri SJ, Sevane JA, et al. *Nature.* 2019;567(7748):399-404. doi:10.1038/s41586-019-1007-8
15. Yang Z, Rodriguez CE. *Proc Natl Acad Sci U S A.* 2013;110(48):19307-19312. doi:10.1073/pnas.1311790110

Disclosures

Study funded by GRAIL, LLC, a subsidiary of Illumina, Inc. All other financial relationships disclosed at abstract submission.

Acknowledgements

Funded by GRAIL, LLC, a subsidiary of Illumina, Inc. Writing and editorial assistance provided by Prescott Medical Communications Group (Chicago, IL).