Revisiting a null hypothesis: exploring the parameters of oligometastasis treatment

Jessica A. Scaborough1,2, Martin C. Tom3, and Jacob G. Scott1,2,4,5

1Translational Hematology and Oncology Research, Cleveland Clinic
2Systems Biology and Bioinformatics Program, Department of Nutrition, Case Western Reserve School of Medicine
3Department of Radiation Oncology, Miami Cancer Institute, Baptist Health South Florida, Miami, Florida
4Radiation Oncology, Cleveland Clinic

In the treatment of patients with metastatic cancer, the current paradigm states that metastasis-directed therapy does not prolong life. This paradigm forms the basis of clinical trial null hypotheses, where trials are built to test the null hypothesis: patients garner no overall survival benefit from targeting metastatic lesions. However, with advancing imaging technology and increasingly precise techniques for targeting lesions, a much larger proportion of metastatic disease can be treated. As a result, the life-extending benefit of targeting metastatic disease is becoming increasingly clear. In this work, we suggest shifting this qualitative null hypothesis, and describe a mathematical model which can be used to frame a new, quantitative null. We begin with a very simple formulation of tumor growth, an exponential function, and use it to show that while any amount of cell kill will extend survival, in many cases the extent is so small as to be unnoticeable in a clinical context or out-weighed by factors related to toxicity and treatment time. Recasting the null in these quantitative terms will allow trialists to design trials specifically to increase understanding of what circumstances (patient selection, disease burden, tumor growth kinetics) can lead to improved OS when targeting metastatic lesions, rather than whether or not targeting metastases extends survival for patients with (oligo-)metastatic disease.

oligometastasis | mathematical oncology | radiation therapy | cancer

Correspondence: scottj10@ccf.org

Introduction

In the treatment of patients with metastatic cancer, the current paradigm states that targeted treatment of metastatic lesions does not prolong life. This paradigm forms the basis of clinical trial null hypotheses, where trials are built to test the null hypothesis: patients garner no overall survival (OS) benefit from targeting metastatic lesions.

The development of distant metastases is the forerunner of cancer-related death (1–3). A Hallmark of Cancer, the dissemination of cancer cells from their origin to distant sites results from a complex cascade of biological events, which may subsequently allow for even more efficient tumor propagation (4–6). Eradicating the body of as much metastatic disease as feasibly possible to halt said process is a natural inclination. Yet, historically, a guiding principle in treating cancer has been that targeting metastatic lesions leads to poor outcomes, because the treatment is either too late or too moribund. However, with advancing imaging technology and increasingly precise techniques for targeting lesions, a much larger proportion of metastatic disease can be treated. As a result, the life-extending benefit of targeting metastatic disease is becoming increasingly clear.

Metastatic stage is typically described as a binary variable in a clinical setting, either present or not (M0 or M1), although certain cancer subtypes (e.g. colon, prostate) now have more gradation in classifying a patient’s metastatic stage (7). The term “oligometastatic state” was first described in 1995 as an intermediary between localized and widespread metastatic disease where metastasis-directed treatment has the potential to be curative (8). Since then, results from several exploratory studies and randomized controlled trials using metastasis-directed therapy in such patients have accumulated to support its existence (9, 10).

Consensus definitions have since been proposed to further refine subgroups of oligometastasis (11–13). For example, the distinction between oligometastatic disease at presentation versus the development of oligometastatic disease following definitive treatment of non-metastatic cancer have been designated “synchronous oligometastases” and “metachronous oligorecurrence,” respectively. “Oligoproggression” describes growth of few metastases in the setting of otherwise stable (or responsive) disease whilst undergoing systemic therapy, and “oligopersistence” is characterized by having several lesions which have a poorer response to systemic therapy than others. Intra-patient heterogeneity often complicates diagnostics even further, where some lesions respond to therapeutics while others persist. These designations (and many more not listed) underscore the complexity with which researchers and clinicians are coming to understand this disease state.

In addition to refining the term “oligometastatic,” clinicians have examined the benefit of treating patients with oligometastases (27, 28). The implicit null hypothesis of these investigations, that targeting metastatic disease does not provide a life-extending benefit, stems from the current paradigm of metastatic cancer treatment. Table 1 summarizes the results of some of these recent phase II and III clinical trials, demonstrating that this null hypothesis is frequently (but not always) refuted. Even accounting for known positive publication bias (29, 30), there is substantial evidence that supports a changing paradigm in the treatment of oligometastatic patients. However, despite many studies showing a significant increase in overall survival (OS) when metastatic lesions are targeted, the null hypothesis in ongoing clinical trial planning has not changed.

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
| Citation | CT Phase | Primary Location | Results | Description |
|----------|----------|-----------------|---------|-------------|
| (14, 15) | II       | NSCLC           | Positive for PFS and OS | In the Gomez et al. trial, treating oligometastases (≤3 non-primary lesions) demonstrated significant improvement in PFS and OS compared to maintenance therapy alone. |
| (16)     | II       | NSCLC (EGFR/ALK negative) | Positive for PFS | In the trial by Iyengar et al., targeting the primary with radiotherapy and oligometastases with SBRT followed by maintenance chemotherapy provided significantly improved progression-free survival compared to maintenance chemotherapy alone. |
| (17, 18) | II       | Variety         | Positive for OS | In the “SABR-COMET” trial, treating all sites of oligometastatic cancer with SABR demonstrated significantly improved OS compared to standard palliative treatment. |
| (19)     | II       | Prostate (hormone sensitive) | Positive for composite of progression metrics | In the “ORIOLE” trial, treating all sites of oligometastases with SABR led to improved outcomes measured by 6-month rate of progression (by PSA, imaging, symptoms, androgen-deprivation therapy initiation, and survival) when comparing to observation alone. |
| (20)     | II       | Prostate        | Positive for ADT-free survival | In the “STOMP” trial, in patients with metastatic oligometastases, using metastasis-directed therapy (SBRT or surgery) provided longer ADT-free survival compared to surveillance alone. |
| (21, 22) | II       | CRC             | Positive for OS | In the “EORTC 40004” trial, treating liver metastases (<10, no extrahepatic disease) with RFA, systemic treatment, and +/- resection led to long-term OS improvement compared to systemic treatment alone. |
| (23)     | II       | ES-SCLC         | Positive for PFS, negative for OS | In the “RTOG 9301” trial, treating oligometastases with PCI and consolidative radiotherapy to both the chest and metastases did not improve OS and did delay progression, compared to PCI alone. |
| (24)     | III      | Prostate        | Positive for PSA progression, negative for OS | In the “HORRAD” trial, in patients with metastases to the bone (any amount), providing radiotherapy to the prostate along with ADT did not improve OS and did delay time to PSA progression, compared to ADT alone. Exploratory subgroup analysis suggested patients with ≤4 bone metastases may benefit from prostate radiotherapy. |
| (25)     | III      | Prostate        | Negative for OS in complete group, positive for OS in patients with lower metastatic burden | In Arm H of the “STAMPEDE” trial, radiotherapy to the prostate did not improve OS in unfiltered cohort of patients, compared to lifelong ADT. However, in a pre-specified subgroup analysis, significant OS improvement was observed among those with lower metastatic burden. |
| (26)     | III      | Nasopharynx     | Positive for PFS and OS | In a trial by You et al., the addition of locoregional radiotherapy to the primary improved OS and PFS compared to chemotherapy alone in patients with (oligo- and poly-) metastatic nasopharyngeal carcinoma. |

Table 1. A summary of clinical trials that examine the benefit of providing local treatment to patients with oligometastases.

In this work, we suggest shifting this qualitative null hypothesis, and describe a mathematical model which can be used to frame a new, quantitative null. We begin with a very simple formulation of tumor growth, an exponential function, and use it to show that while any amount of cell kill will extend survival, in many cases the extent is so small as to be unnoticeable in a clinical context or out-weighted by factors related to toxicity and treatment time. Recasting the null in these quantitative terms will allow trialists to design trials specifically to increase understanding of what circumstances (patient selection, disease burden, tumor growth kinetics) can lead to improved OS when targeting metastatic...
lesions, rather than determining whether targeting metastases can extend survival for patients with (oligo-)metastatic disease. We purposely begin with the most simplistic possible mathematical model, considering only total disease burden and doubling time. We do not consider complexities such as space, metastatic locations/connectedness (31), immune interactions or any heterogeneities— all things which could be considered in future iterations, but which make the model less generalizable.

Due to its breadth, the current qualitative null hypothesis may be incorrectly accepted or rejected without a quantitative model to help design optimal patient and treatment parameters. Numerous qualitative and quantitative prognostic factors exist to help identify patients with metastatic disease which is likely to follow a relatively indolent course. For example, with slower disease progression, patients are more likely to derive greater benefit from aggressively targeting their metastases. Other characteristics include the number of lesions and organs involved, the time course of presentation and progression, tumor histology, patient innate and adaptive immunity, and various biological features (32). It is crucial that we parse through which of these patient characteristics can meaningfully affect treatment outcomes in the setting of oligometastasis. By rethinking the null hypothesis of metastatic cancer treatment, research efforts can better serve our patients by bringing a deeper understanding of how well treatment works, who it works best for, and when it is most efficacious, rather than continually testing the implicit null hypothesis.

**Model**

Beginning with a very simple model of tumor growth, an exponential function, we will explore the effect of treatment in scenarios with different growth rates, treatment effectiveness, and timing of the intervention. While this overlooks many of the realities of real human cancers, such as spatial, intra- and inter-tumoral (33–35) heterogeneity, it captures many of the essential aspects of growth (36). Furthermore, in the absence of other specific knowledge, general arguments can be expounded upon, but additional undetermined complexities can severely limit generalizability. Let us then model a tumor of size (cell number), N, beginning with a single cell, and a growth rate, r, as follows:

\[ N(t) = e^{rt}. \]  

To illustrate how the same intervention (removing \( N_c \) cells from the tumor) at different times effects our measure of survival, we plot several growth curves together in Figure 1. The time when each of these curves reaches \( N_T \) is the time of death (\( t_{d,x} \)). The difference (\( \Delta t \)) between the unperturbed time of death (\( t_{d,1} \)) and each subsequent example intervention (e.g. \( \Delta t = t_{d,2} - t_{d,1} \)) is the increase in survival. We note that the earlier the intervention occurs (smaller \( N_d \)), the greater the \( \Delta t \) and, therefore, increase in survival. This is also true if we kill more cells (i.e. \( N_c \) increases).

While Figure 1 considers how a single intervention will effect the “same” tumor, Supplementary Figure 1 explores the effect of altering tumor growth rate, \( r \), on \( \Delta t \) after the same intervention. This figure adds a faster tumor growth curve, in addition to the curve seen in Figure 1. The same intervention (removal of \( N_c \) cells) occurs at the same time points as the slower curve, yet the faster growing tumor has a smaller resulting changes in survival time (\( \Delta t_f \)) compared to the slower growing tumor (\( \Delta t_s \)).

Next, we will examine the analytical relationship between the change in survival (\( \Delta t \)) to the other parameters (\( r, N_c, N_d \)). This requires examining two tumor growth curves, one with unperturbed growth starting at \( N_d \) and the other with perturbed growth beginning at \( (N_d - N_c) \). In other words, the perturbed curve will have the same growth characteristics as the unperturbed curve, but it will have \( N_c \) cells removed as “treatment.” Then, we will calculate the offset of time between the two curves when they reach \( N_T \), i.e. \( \Delta t \).

Graphically, we are asking how large the difference on the time axis is between where the treated and untreated curves intersect with \( N_T \) (the black dashed line), denoted by colored circles in Figure 1 and Supplementary Figure 1. Mathematically, we find the difference between \( t_{d,1} \) and \( t_{d,2} \): i.e. \( \Delta t \) when \( (N_d)e^{rt_1} = (N_d - N_c)e^{rt_2} = N_T \). This relation is:

\[ \Delta t = \frac{1}{r} \ln \left( \frac{N_d}{N_d - N_c} \right). \]  

The observations from before are maintained: slower growing tumors (smaller \( r \)), more effective interventions (increasing \( N_c \)), and lower burden at time of treatment (lower \( N_d \)) make for a larger survival benefit, as we have intuited.

Given the intuitive nature of these results, one may question what the value of such a model is. First, this model allows for the quantitative exploration of what was previously an exclusively qualitatively described phenomenon. This allows for formal interrogation of the individual values of each parameter, a crucial step in quantitative reasoning during clinical trial design. In doing so, a framework for parameter estimation can help trialists perform sensible power calculations. This would require measuring distributions of each of these parameters as it is clear that heterogeneity (and uncertainty) exists in each. Further, this would allow for error propagation in addition to power calculations. With recent work trying to incorporate toxicity into survival analyses in radiation oncology (37), we have the opportunity to formally probe the balance between benefit and harm in this setting. Most importantly however, it will remove the confusion cre-
Fig. 1. Change in OS is modulated by when an oligometastasis-directed intervention occurs and the effectiveness of the intervention. We plot an illustrative exponential growth curve from equation 1 in black. At three different times, we subtract \( N_c \) cells from the curve to simulate an oligometastasis-directed intervention (orange markers), and the tumor continues to grow at the original rate from the new size. These subsequent tumors then grow and eventually intersect an arbitrary threshold cell (a surrogate for maximum tolerated disease burden) number (\( N_T \) - dashed horizontal line), there we can then determine the change in survival (vertical black lines, inset). The change in this time represents the \( \Delta t \) for each intervention. n.b. These are not realistic parameters, but instead serve to illustrate the (qualitatively conserved) phenomenon.

Figure 2 demonstrates a benefit of using a quantitative model with a sensitivity analysis to help us better understand the areas of the (very simplified) parameter space, a range of possible parameter values, where the greatest opportunities lie. Given that this is a simple exponential relation, the change in survival is monotone (always up or down) in each parameter. However, as the tumor growth curves are nonlinear, we chose to plot the sensitivity analysis on a log-log plane to improve the visualization of changes in parameter values.

As we do not currently have known values for these parameters, exploring a large sweep of values can be instructive. We consider a continuous range for \( N_c \) in \([0, N_d]\), where \( N_c = 0 \) represents no intervention and \( N_c = N_d \) represents a cure. In these cases, \( \Delta t = 0 \) and \( \Delta t = \infty \), respectively. In Figure 2, we will consider four discrete examples of values for \( r \), as this parameter’s effect is monotone (where a case with lower \( r \) always derives more benefit from oligometastasis-directed therapy than a case with higher \( r \)).

It is also important to note that this parameter is likely modifiable with chemo- or targeted-therapy: something we do not consider here, but would be a straightforward extension. This example will consider growth rates which correspond to tumor doubling times of 100, 200, 300 and 400 days. These could represent tumors such as small cell lung cancer in the fast extreme or prostate cancer in the slow extreme. Figure 2 shows this analysis, with isoclines shown in black to denote lines of equal effect. These curves demonstrate that any increase in \( N_c \) (more cell kill per intervention, “up” on the y-axis) and/or decrease in \( N_d \) (earlier intervention, “down” on the x-axis) increases the OS benefit. It is interesting to note that the movements (i.e. \( N_c \) up and \( N_d \) down) mirror the historical trend: improvements in detection of oligometastasis via anatomic or functional imaging have slowly pushed \( N_d \) lower over the years and the ability to safely (using SBRT...
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Fig. 2. The benefit of oligometastasis-directed therapy depends monotonically on the amount of cells killed, the tumor burden, and tumor doubling time. We plot four orders of magnitude of both $N_c$ and $N_d$ on a log scale. The color represents the predicted number of days of OS benefit for each combination of $N_c$ and $N_d$. Each of the four subplots represents a different “intrinsic” biology, modeled by different tumor doubling times. A $t_d$ of 100, 200, 300, and 400 days corresponds to a growth rate, $r$, of 0.0069, 0.0035, 0.0023, and 0.0017, respectively. Contour lines are shown for ease of comparison. A selection of trials from Table 1 are represented by red circles based on estimations of $N_d$, $N_c$, $r$, and $t_d$ for each trial.

Clinical correlation

In order to demonstrate how clinical trial design can explore the parameter space of this tumor growth model, we will review some recent clinical trials, which are also listed in Table 1. This discussion reviews illustrative examples, and is not an exhaustive list of all clinical trials which test the benefit of targeting oligometastases. For many trials, we will estimate where design falls in the parameter space of Figure 2, and discuss how trial design can test the effects of altering one or more parameters (i.e. $N_d$, $N_c$, or $r$).

In a phase II trial by Gomez et al., 49 patients with oligometastatic ($\leq 3$ metastases) non-small cell lung cancer (NSCLC) without progression after first-line systemic therapy were randomized to either maintenance systemic therapy/surveillance or local consolidative therapy (LCT) to all sites of residual disease via surgery or radiotherapy. After interim analysis demonstrated a substantial PFS benefit with LCT, the trial was closed early and allowed for crossover to the LCT arm (14). With additional follow up, and despite crossover, LCT was associated with improved OS of 41.2 months vs 17.0 months (15). We placed this trial in the top right subplot of Figure 2, due to the relatively fast growth rate of NSCLC, minimal tumor burden ($\leq 3$ metastases), and large $N_c$ using radiotherapy or surgery.
The SABR-COMET study was a screening phase II trial which randomized 99 patients with oligometastatic disease to standard palliative therapy with or without stereotactic ablative radiotherapy (SABR) to all metastatic lesions. The primary endpoint was OS, which was initially improved with the addition of SABR from 28 months to 48 months (18). With additional follow up, results were even more substantial with a median OS of 50 months using SABR versus 28 months in the control arm (38). As this trial includes tumors of many histologies, we cannot place the positive results in a single subplot of Figure 2, but doing so post hoc patient by patient would be illustrative.

In the phase II EORTC 40004 trial, 119 patients with fewer than 10 unresectable colorectal liver metastases and no extrahepatic disease were randomized to systemic therapy with or without local therapy using RFA (with or without resection). Although the primary endpoint of 30 month OS was not met, longer follow up led to improved OS with RFA from 40.5 months to 45.6 months (22). With a relatively slow growing tumor sub-type, a large Nt, and a moderate OS benefit, we estimated this clinical trial to fall in the bottom left subplot of the model’s parameter space found in Figure 2.

The largest study was Arm H of the STAMPEDE trial, which was a phase III trial of 2061 patients with metastatic prostate cancer randomized to androgen deprivation therapy with or without definitive radiotherapy to the prostate. Pre-specified subgroup analysis demonstrated no benefit to the addition of prostate radiotherapy among those with a high metastatic burden, defined as either visceral metastases or ≥ 4 bone metastases with ≥ 1 outside of the vertebral bodies or pelvis. However, in the group of 819 patients with a low metastatic burden, radiotherapy to the prostate improved three-year OS from 73 percent to 81% (25). In relation to our model, this is equivalent to assuming that the two groups (high and low metastatic burden) have different Nt at the time of treatment, but experience the same Nc. It should be noted that unlike other trials discussed, local therapy was delivered only to the primary site, but not the metastatic sites, suggesting a benefit to cytoreduction. The estimated parameter space position of these two subgroups (high metastatic burden and low metastatic burden) is found in the bottom right subplot of Figure 2.

In the ORIOLE trial, patients with metachronous oligometastatic prostate cancer with ≤ 3 sites as detected by conventional imaging were randomized to surveillance of SABR to all sites (19). The primary endpoint was a composite of disease progression metrics at 6 months, which was improved with SABR at 19% versus 61% in the control arm. Interestingly, a subgroup of patients underwent advanced imaging with PSMA PET, which has demonstrated greater sensitivity in detecting prostate cancer metastases (putatively lowering Nt) (39). Among those patients where all PSMA PET avid sites were treated, the 6 month progression rate was just 5% compared to 38% in those with untreated sites. This subgroup analysis further supports that advanced imaging can better identify metastases and treating all sites improves outcomes. By utilizing a more sensitive technology in detecting (and therefore targeting) metastases, we see that a greater Nc increases OS, even if Nt remains the same. We estimate the parameter space for this subgroup analysis in the bottom right subplot of Figure 2.

Not all trials have demonstrated benefit to the addition of metastasis-directed therapy. For example, RTOG 0937 was a phase II study of 86 patients with extensive stage small cell lung cancer with at least a partial response to chemotherapy and 1-4 extracranial metastases who were randomized to prophylactic cranial irradiation with or without consolidative radiotherapy to the chest and all metastatic sites. The primary endpoint of one-year OS was not significantly different; 60% in the control arm and 51% in the consolidative radiotherapy arm (23). This negative result is estimated to be in the top left subplot of Figure 2, due to the rapid growth of SCLC. Here, this model would have still been useful in predicting the outcome of this trial, as a power calculation could demonstrate that the noise in the data and small predicted effect size would require a much greater sample size to demonstrate a significant change in OS.

Conclusions

In this work, we have used a simple exponential model of tumor growth to demonstrate why recent improvements in metastasis detection and treatment may allow us to reconsider the null hypothesis when treating patients with oligometastases. Specifically, more sensitive techniques to localize metastases, as seen with PSMA imaging, allow clinicians to increase how many tumor cells are removed, Nc, when considering patients at similar stages. When used for surveillance, these imaging techniques can decrease the size of the tumor at treatment, Nt, potentially leading to drastically improved OS. Next, advancements in the ability to administer local therapy to all sites of disease with surgical resection, radiotherapy, and/or ablative procedures such as radiofrequency ablation (RFA) has allowed for more effective, precise eradication of metastatic lesions with less associated morbidity. Furthermore, novel immuno- and targeted-therapies can likely decrease the growth rate, r, of tumors. Finally, it is important to note that the model demonstrated in this work is not a perfect representation of tumor growth and treatment, as it fails to consider intratumoral heterogeneity, metastasis location, and the inherent risks of treatment. However, because of its simplicity, this model provides a foundation exploring the current parameter space, while allowing researchers to add complexity as they see fit.

A mathematical model provides the distinct advantage of testing quantitative hypotheses to optimize the treatment of patients with oligometastases. Parameter selection regarding number of oligometastases, measurements of tumor burden, and efficacy of treatment options can be examined with robust hypotheses born from simulated results. Additionally, with increased translation between the bench and bedside, some of model parameters (e.g. , tumor growth rate) may be inferred using serial tumor biopsies, in vitro, or in silico modeling. Furthermore, Bayesian adaptive clinical trials can
utilize these results during interim analyses to update the prior probability, predicted probability of success, and power calculations [40, 41].

Imaging and therapeutic advancements have provided us with the opportunity to revisit the implicit null hypothesis when treating patients with oligometastases. This null hypothesis states that targeting oligometastases does not provide life-extending benefit. There are minimal published clinical trial results that demonstrate this null hypothesis not being rejected; however, this is likely due to publication bias where positive results are more likely to be published, not simply because this null hypothesis has always been rejected (29, 30).

The clinical trials we discuss have necessarily sought to examine the fundamental idea that oligometastatic lesions should only be targeted for palliative care. Refuting this null hypothesis was crucial, as the earlier state of cancer imaging and treatment established that targeting oligometastases either occurred too late or caused too much harm. Yet, as quantitative models of tumor growth and the knowledge of how metastatic detection and treatment have evolved, we believe that clinical trials can now provide an even greater benefit by adjusting the implicit null hypothesis. Instead of demonstrating that targeting oligometastases provides benefit compared to surveillance or systemic therapy alone, rigorous hypothesis can be tested surrounding targeted treatment options, treatment timing, the sensitivity of imaging detection, and overall tumor burden.

### Code Availability

All manuscript code used to create mathematical models and figures in this manuscript may be found on GitHub at https://github.com/jessicascarborough/oligo-null.

### Bibliography

1. Christine L Chaffer and Robert A Weinberg. A perspective on cancer cell metastasis. Science, 331(6062):1559–1564, 2011.
2. Hanna Dilaks, Michael S Rogers, and Oddbjörn Sivaram. Are 90% of deaths from cancer caused by metastases? Cancer Medicine, 8(12):5574–5576, 2019.
3. Thomas N Seyfried and Leanne C Huysentruyt. On the origin of cancer. Critical reviews in oncogenesis, 18(1–3):11, 2013.
4. Douglas Hanahan and Robert A Weinberg. The hallmarks of cancer. cell, 100(1):57–70, 2000.
5. Jacob Scott, Peter Kuhn, and Alexander RA Anderson. Unifying metastasis—integrating intravasation, circulation and end-organ colonization. Nature Reviews Cancer, 12(7):445–456, 2012.
6. Scott Valastyan and Robert A Weinberg. Tumor metastasis: molecular insights and evolving paradigms. Cell, 147(2):275–292, 2011.
7. Mahul B Amin, Frederick L Greene, Stephen B Edge, Carolyn C Compton, Jeffrey E Gerh- shenfeld, Robert K Brookland, Laura Meyer, Donna M Gress, David R Byrd, and David P 504. Winchester. The eighth edition ajcc cancer staging manual: continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging. CA: a can- cer journal for clinicians, 67(2):93–99, 2017.
8. Samuel Heilman and Ralph R Weichselbaum. Oligometastases. Journal of Clinical Oncol- ogy, 13(1):8–10, 1995.
9. Sean P Podroka, Nikolai N Khodarev, Lei Huang, Ahineefti Uppal, Sean C Wightman, Sabha 510. Ganai, Nora Joseph, Jason Pitt, Miguel Brown, Martin Forde, et al. integrated molecular subtyping defines a curable oligometastatic state in colorectal liver metastasis. Nature communications, 9(1):1–8, 2018.
10. Julian C Hong, Dendra N Ayala-Peacock, Jason Lee, A William Blackstock, Paul Okunieff, Max W Sung, Ralph R Weichselbaum, Johnny Kao, James J Urbani, Michael T Milano, et al. Classification for long-term survival in oligometastatic patients treated with ablative radiotherapy: a multi-institutional pooled analysis. PLoS one, 13(4):e0191549, 2018.
11. Andreas G Steuber and Stefan Heiland. Oligometastases revisited. Nature reviews Clinical oncology, 8(6):378, 2011.
12. Matthias Guikkenber, Yolanda Lieveens, Angelique B Bourma, Laurence Collette, Andre Dekker, M delSouza Nandita, Anne-Marie C Dingesman, Beatrice Fournier, Coen Hur- kens, Chloé-Frédéric E Lecouvet, et al. Characterisation and classification of oligometastatic disease: a european society for radiotherapy and oncology and european organisation for research and treatment of cancer consensus recommendation. The Lancet Oncology, 21 (1):e18–e28, 2020.
13. Yolanda Lieveens, Matthias Guikkenber, Daniel Gomez, Morten Hoyer, Piusneeth Iyengar, Isabelle Kindt, Alejandra Mendez Romero, Daan Nevens, David Palma, Catherine Park, et al. Defining oligometastatic disease from a radiation oncology perspective: An estro- astro consensus document. Radiotherapy and Oncology, 2020.
14. Daniel R Gomez, George R Blumenschein Jr, J Jack Lee, Mike Hernandez, Rong Ye, D Ross Camidge, Robert C Doebbe, Ferdinandos Skoulidis, Laurie E Gasper, Don L Gibbons, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. The lancet oncolog- y, 17(12):1672–1682, 2016.
15. Daniel R Gomez, Chad Tang, Jianjun Zhang, George R Blumenschein Jr, Mike Hernandez, J Jack Lee, Rong Ye, David A Palma, Alexander V Louise, D Ross Camidge, et al. Local consolidative therapy vs. maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer: long-term results of a multi-institutional, phase ii, randomized study. Journal of Clinical Oncology, 37(18):1558–1565, 2019.
16. Punteneh Iyengar, Zabi Wardak, David E Gerber, Vasu Tumati, Ch. Ahm, Randall S Hughes, Josephon E Bowell, Naga Chendrimada, Lucien Netti, Kenneth W Orgel, et al. Genoma- dive therapy for limited metastatic non-small-cell lung cancer: A phase 2 randomized clinical trial. JAMA oncology, 4(1):e173501–e173501, 2018.
17. David A Palma, Cornelis JA Klaxboek, George B Rodrigues, Max Dahle, Michael Lock, Brian Emko, Robert Olijon, Stuart Gaede, Alexander V Louise, Con- nelisis JA Klaxboek. Laim Muirzy, Michael B Rodrigues, Brian P Yemekic, et al. Stereotactic ablative radiotherapy for comprehensive treatment of oligometastatic tumors (sabr-comet): study protocol for a randomized phase ii trial. BMC cancer, 12(1):305, 2012.
18. David A Palma, Robert Otson, Stephen Horrow, Stewart Gaede, Alexander V Louise, Connelisis JA Klaxboek. Laim Muirzy, Michael B Rodrigues, Brian P Yemekic, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (sabr-comet): a randomised, phase 2, open-label trial. The Lancet, 393(10185):2051–2058, 2019.
19. Ryan Philips, William Yue Sh, Matthew Deek, Noura Radwan, Su Jin Lim, Emmanuel S Antonarakis, Steven P Rowe, Ashley E Ross, Michael A Gorin, Curtland Deville, et al. Out- comes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: the oriole phase 2 randomized clinical trial. JAMA oncology, 6(5):650–659, 2020.
20. Pet Ost, Dries Ruynder, Karel Decaestecker, Valerie Fonteyne, Nicolaas Lumen, Aurelie DeBlijcker, Birte Lambert, Loukie Delrue, Renée Buljntje, Tom Claes, et al. Surveillance or metastesis-directed therapy for oligometastatic prostate cancer recurrence: a prospec- tive, randomised, multicenter phase i trial. Journal of Clinical Oncology, 2017.
21. T Ruers, C Punt, F Van Coevorden, JPEN I Borel-Rinkes, JA Ledermann, Graeme Poston, Wolf Bechstein, MA Lentz, M Maurer, et al. Radiotherapy ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: results of a randomized phase i trial. JNCI: Journal of the National Cancer Institute, 109(5):dj015, 2017.
22. Elizabeth M Gore, Chen Hu, Alexander Y Sun, Daniel F Grimm, Suresh S Ramalingam, Neal E Duriau, Kristin A Hogbin, Matthew M Allen, Puneet Iyengar, et al. Randomized phase ii study comparing prophylactic cranial irradiation alone to pro- phylactic cranial irradiation and consolidative extracranial irradiation for extensive-disease small cell lung cancer (ed:sc): Nrg oncology rng007. Journal of Thoracic Oncology, 13(10):1561–1570, 2017.
23. Liselotte MS Beene, Maarten CCM Hulsf, Andre N Vs, Jelko H Zwinderzer, Jos WR Twik, Wim PJ Wiljes, Kari PJ Delaere, R Jeroen A van Moorselaar, Paul CMS Verhagen, and George van Andel. Effect on survival of androgen deprivation therapy alone compared to androgen deprivation therapy combined with concurrent radiation therapy to the prostate in patients with primary bone metastatic prostate cancer in a prospective randomised clinical trial: data from the horrad trial. European urology, 75(3):410–418, 2019.
24. Christopher P Barker, Nicholas D James, Christopher B D wrinkley, Noel W Clark, Alex P Hyland, Paul M Adam, Alastair WS Ritchie, Gerhardt Atton, Simon Chadwick, William Smilt, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (stampeade): a randomised controlled phase 3 trial. The Lancet, 392(10126):2353–2366, 2018.
25. Rui You, You-Ping Liu, Pei-Yu Huang, Xiong Zou, Rui Sun, Yu-Xiao Wang, Yi-Shan Wu, Guo- ping Shen, Hong-Dan Zhang, Chong-Yang Duan, et al. Efficacy and safety of locoregional radiotherapy with chemotherapy vs chemotherapy alone in de novo metastatic nasopharyn- geal carcinoma: A multicenter phase 3 randomized clinical trial. JAMA oncology, 2020.
26. Deepak Sharma, Jin Won Sam, Minh Khuong, Arvind G Mu, Thomas E Smits, Jacqueline P Williams, Edward Messing, and Paul Okune. Is there a favorable subset of patients with prostate cancer who develop oligometastases? International Journal of Radiation Oncology Biology Physics, 104(1):3–10, 2004.
27. David A Palma, Joseph K Salama, Suresh S Ramalingam, Hai Linh L Vu, Danielle MGFir怛, et al. Radiotherapy: a multi-institutional pooled analysis. Journal of Clinical Oncology, 13(4):e0195149, 2018.
29. Ana Milanić, Martina Horvat, and Vesna Šupak Smolčić. Dealing with the positive publication bias: Why you should really publish your negative results. *Biochemia medica: Biochemia medica, 27*(3):447–452, 2017.

30. Mohammad Hassan Murad, Haitao Chu, Lifeng Lin, and Zhen Wang. The effect of publication bias magnitude and direction on the certainty in evidence. *BMJ evidence-based medicine, 23*(3):84–86, 2018.

31. Jacob G Scott, David Basanta, Alexander RA Anderson, and Philip Gerlee. A mathematical model of tumour self-seeding reveals secondary metastatic deposits as drivers of primary tumour growth. *Journal of The Royal Society Interface, 10*(82):20130011, 2013.

32. Sean P Pitroda and Ralph R Weichselbaum. Integrated molecular and clinical staging defines the spectrum of metastatic cancer. *Nature Reviews Clinical Oncology, 16*(9):581–588, 2019.

33. Andriy Marusyk and Kornelia Polyak. Tumor heterogeneity: causes and consequences. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer, 1805*(1):105–117, 2010.

34. Jacob G Scott, Alexander G Fletcher, Alexander RA Anderson, and Philip K Maini. Spatial metrics of tumour vascular organisation predict radiation efficacy in a computational model. *PLoS computational biology, 12*(1):e1004712, 2016.

35. Jacob G Scott, Anders Berglund, Michael J Schell, Ivaylo Mihaylov, William J Fulp, Binglin Yue, Eric Welsh, Jimmy J Caudell, Kamran Ahmed, Tobin S Strom, et al. A genome-based model for adjusting radiotherapy dose (gard): a retrospective, cohort-based study. *The Lancet Oncology, 18*(2):202–211, 2017.

36. Philip Gerlee. The model muddle: in search of tumor growth laws. *Cancer research, 73*(8):2407–2411, 2013.

37. Jacob G Scott, Geoffrey Sedor, Michael W Kattan, Jeffrey Peacock, G Daniel Grass, Eric A Mellon, Ram Thapa, Michael Schell, Anthony Waller, Sean Poppen, et al. Optimizing clinical outcome and toxicity in lung cancer using a genomic marker of radiosensitivity. *medRxiv, 2020.*

38. David Palma, Robert Olson, Stephen Harrow, Stewart Gaade, Alexander V Leue, Cornelis Haasbeek, Liam Mulloy, Michael Lock, George Rodrigues, Brian Yaremko, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: Long-term results of the sabr-comet phase ii randomized trial. *medRxiv, 2020.*

39. Finn E von Eyben, Maria Picchio, Rie von Eyben, Handoo Rhee, and Glenn Baum. 68ga-labeled prostate-specific membrane antigen ligand positron emission tomography/computed tomography for prostate cancer: a systematic review and meta-analysis. *European urology focus, 4*(5):686–693, 2018.

40. Matthew A Psioda and Joseph G Ibrahim. Bayesian clinical trial design using historical data that inform the treatment effect. *Biostatistics, 20*(3):400–415, 2019.

41. Donald A Berry. Bayesian clinical trials. *Nature reviews Drug discovery, 5*(1):27–36, 2006.
Supplementary Information

Supplementary Fig 1. Change in OS is modulated by tumor growth rate, intervention timing, and intervention efficacy. Top: We plot two illustrative exponential growth curves from equation 1 in black, using a faster (dotted line) and slower (solid line) growth rate, \( r \). The slower growth rate is the same curves shown in Figure 1. At three different time points, we subtract \( N_c \) cells from the two curves to simulate an oligometastasis-directed intervention, and the tumor continues to grow at the original rate from the new size. These subsequent tumors then grow and eventually intersect an arbitrary threshold cell (a surrogate for maximum tolerated disease burden) number (\( N_T \) - dashed horizontal line). Bottom: We plot two expanded windows of the above plot, showing greater detail of the faster (left, dotted) and slower (right, solid) growth curves as they reach \( N_T \). In these plots, we can then determine the change in survival (vertical black lines). The change in this time represents the \( \Delta t_f \) and \( \Delta t_s \) for each intervention in the fast and slow curves, respectively. Notably, the x-axis for the faster (left, dotted) growth curves accounts for fewer days, despite having the same relative length as the x-axis for the slower (right, solid) growth curves. This was necessary in order to annotate the smaller \( \Delta t_f \) for the faster growth curves.