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Treating Cancer as an Invasive Species

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Abstract

To cure a patient's cancer is to eradicate invasive cells from the ecosystem of the body. However, the ecological complexity of this challenge is not well understood. Here we show how results from eradications of invasive mammalian species from islands—one of the few contexts in which invasive species have been regularly cleared—inform new research directions for treating cancer. We first summarize the epidemiological characteristics of island invader eradications and cancer treatments by analyzing recent datasets from the Database of Invasive Island Species Eradications and The Cancer Genome Atlas, detailing the superior successes of island eradication projects. Next, we compare how genetic and environmental factors impact success in each system. These comparisons illuminate a number of promising cancer research and treatment directions, such as heterogeneity engineering as motivated by gene drives and adaptive therapy; multi-scale analyses of how population heterogeneity potentiates treatment resistance; and application of ecological data mining techniques to high-throughput cancer data. We anticipate that interdisciplinary comparisons between tumor progression and invasive species would inspire development of novel paradigms to cure cancer.

Introduction

Improvements in DNA and RNA sequencing technology have transformed our knowledge of cancer [1,2], yet they have also revealed a daunting ecological complexity. The cancer ecosystem includes genetically heterogeneous cancer cells and localized microenvironments in a web of interactions among tumor, immune, and stromal cells [3,4], and this ecosystem interfaces with the greater environment of the patient's body. The complexity of the cancer ecosystem has made it difficult to prioritize cancer cell features for targeted treatment. To solve this challenge, studies of pest animal ecosystems can provide valuable insights. Invasive mammalian species, particularly rats, have caused serious ecological damage and extinguished native species on islands around the world, and hundreds of projects to eradicate these invaders have been attempted globally [5]. Notably, the Predator-Free New

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Zealand movement has set a goal of eliminating rats from the country's archipelago by 2050 in order to save native fauna from this efficient predator and allow ecosystem recovery [6]. Despite the enormous differences in scale, we argue that a systems approach comparing island restoration to cancer therapy will elucidate factors that influence the success of different treatments.

Epidemiologically, invasive species and cancers share similar properties [7,8] in terms of invasion, growth, spread, treatment, and outcome, as shown in Fig. 1. The isolated naive environments of islands have made them key systems for studying and repairing ecologies disrupted by invasive species. Invading rats typically arrive on islands as small populations or even single pregnant individuals via boats or by swimming, analogous to cancers developing within the body from a single tumor cell. For both invasive species and cancers, these initial populations then grow until they are detected, at which point action must be taken as soon as possible to halt their expansion.

Epidemiological comparison of invasive species and cancer

Multiple methods have been deployed to eradicate invasive species and to treat cancer. We have assessed the prevalence of common strategies (Fig. 2A, 2B, and Supplementary Table S1) by analyzing the Database of Island Invasive Species Eradications (DIISE) [9] and The Cancer Genome Atlas (TCGA) [1]. Statistics for the six most frequently targeted mammalian clades in the DIISE, i.e. rodent, lagomorph (rabbit and hare), canid (dog and fox), felid (cat), mustelid (mongoose and weasel), and ungulate (hoofed mammals), are shown in Fig. 2A. These eradication projects are undertaken based on available funding [10] and socio-legal capacity, making uninhabited islands the preferred target [11]. The most prevalent eradication strategies are trapping, hunting, and toxicant, with toxicant being the most used method (67% of all attempts). Rodents are the most frequently targeted group (735 eradications, 64% of all attempts), with most cases treated by toxicant (94% of attempts). Similarly, we analyzed 22 tumor types from TCGA (minimum cohort size of 50 patients), and stratified them by treatment strategy. Common non-surgical cancer treatments include chemotherapy, radiotherapy, immunotherapy, and targeted molecular therapy (Fig. 2B), with chemotherapy and radiotherapy being the most prevalent cancer treatments.

There are parallels between the strategies for eradicating invasive species from islands [5] and treating cancer in the human body [4]. For example, rodent toxicants are broadly administered either aerially or via ground-based devices, analogous to the treatment of cancer by chemotherapy through the bloodstream. Hunting is similar to cancer immunotherapy, as each method targets elusive quarry in a highly specific fashion. Animal trapping and cancer targeted molecular therapy are each moderately specific and complement broad-spectrum methods. Moreover, in each system it is vital that eradication methods avoid side effects that would be detrimental to native fauna [12] or patient health.

The success rates of common strategies for invasive species eradication and cancer treatment are summarized in Fig. 2C and 2D. Success rates have been high for all invasive species–treatment combinations (Fig. 2C), with a median success rate of 91% (confidence interval 80–97%, Jeffreys binomial proportion test at 95% confidence). Some species–treatment

combinations have been particularly successful, e.g. canid–trapping has had a 100% success rate (CI 86–100%) and even the least successful have worked well, i.e. felid–hunting has had a 69% success rate (CI 44–87%). These eradications can be confidently ascertained by surveying islands several generations after treatment, e.g. two years for rats, providing ample time for populations to rebound from small numbers [13]. For comparison, cancer treatment success rates are shown in Fig. 2D. The median of the five-year survival rate for combinations of cancer type–primary nonsurgical treatment is 52% (CI 35–65%; beta product procedure at 95% confidence [14]). Testicular germ cell tumors treated with chemotherapy have the best outcome, as 100% of patients survive (CI 88–100%), while esophageal carcinoma treated with chemotherapy/radiotherapy has the worst outcome, as 0% of patients survive. Some cancer types have high survival rates across multiple different treatments, notably testicular germ cell tumors, prostate adenocarcinoma, thyroid carcinoma, and breast invasive carcinoma. Conversely, others have low survival regardless of the treatment used, e.g. glioblastoma multiforme has a survival rate <8% for every primary therapy used. Overall, eradication success rates are higher and more stable across different island invasive species, whereas success rates are lower and vary more across cancers.

Factors impacting invasive species and cancer eradication

It is informative to compare and contrast the factors that affect the success of eradication and treatment in these systems. Here we highlight several aspects, namely: distinctiveness between the invader and native species; effectiveness of common treatments across diverse invaders; intrapopulation heterogeneity of the invader; and environmental interactions (Table 1). We have chosen these factors because current measurements allow them to be quantitatively compared, though more comprehensive descriptions of each system can be found elsewhere [4,15].

Distinctiveness between the invader and native species is critical to enable specific eradication of the invader with minimal impact to the host ecosystem. At the genetic level, there is greater divergence between invasive mammals and the native species they threaten, which are typically birds, than there is between a patient's cancer cells and normal cells. Rats and birds have millions of coding sequence differences [16] while cancer and normal cells differ by only 10–1000 somatic coding point mutations [17]. This makes treatment specificity easier to achieve for rat invasions, and indeed anticoagulant/citric acid cycle toxicant strategies have often succeeded in controlling or eradicating rats while permitting native bird species to re-expand [18]. Optimization for feeding preferences, which may derive from genetic differences, has been important to this specificity, e.g. use of compressed cereal bait matrices with green coloring reduces toxicant appeal to most birds. Meanwhile, non-specific side effects limit most cancer treatments.

The effectiveness of common treatments across diverse invaders differs substantially between invasive mammals and cancers. A wide range of invasive mammalian species have similar responses to the most commonly applied toxicants despite tens of millions of years of evolutionary divergence, as exemplified by the species listed in Fig. 2. On the other hand, cancers have more variable responses to chemotherapy and radiotherapy, which are the most common treatments, even though any two tumors have comparatively low evolutionary

divergence. Cancers from different patients are distinguished by the germline differences between the patients (~10^5 coding mutations) and the cancer somatic mutations (~10^3 coding mutations), which sum to fewer mutations than distinguish mammals and birds. Thus, interpatient tumor diversity does not preclude successful pan-cancer treatments. The greater constraint is that such pan-cancer effectiveness must be achieved with minimal impact on normal cells.

Intrapopulation genetic heterogeneity is fundamental to survival for both island invaders and treated cancer cells. Cancers are made up of multiple subclones with distinct mutations that may confer resistance to treatment [19], and high intratumoral heterogeneity provides more opportunities for resistance. Invasive rodents are subject to the same dynamics but evolve resistance less frequently than cancers do [20]. This may be due to the low population sizes of rodents, as there are on average 10^3 rats on islands for which exterminations have been attempted [21] compared to the 10^9 cells in a 1 cm^3 neoplasm [22]. Consistent with this trend, eradication attempts on larger islands have had lower success rates (82%) than on smaller islands (91%) (Fisher's exact test $P = 4.7\times10^{-4}$, DIISE database), but both small and large islands have better outcome rates than median cancer survival. Rapid mutation rates also potentiate resistance in cancer, as the cancer mutation rate (10^{-7}/bp/generation) is higher than that for rats (10^{-8}/bp/generation) [16], in addition to cancer cells having much shorter generation times.

Environmental interactions also distinguish invading species and cancers. An underlying reason is that cancers usually originate in the tissues in which they develop, whereas invasive species immigrate to naive islands. As a result, cancer cells–like native cells–have strong interactions with the local microenvironment. For example, fibroblasts influence chemoresistance of cancer cells, and the immune system has major impacts on patient survival [23]. Environmental factors play less of a role for invasive rats than in cancer, as rats are known for their ability to live in diverse biomes. This is also true in the treatment context, as both tropical and temperate islands have rat eradication success rates >80% [15]. Nevertheless, some environmental factors have been found that reduce the success of rat eradication efforts, notably higher temperatures, presence of local agriculture, and presence of species that eat bait (land crabs) or provide alternative food sources (coconut palms). These environmental considerations are also related to cancer metastasis, in which cancer cells grow in the new microenvironment of a different organ. Likewise, rats can swim to other islands more than 1km away. However, nearby islands are not inherently different in environment than the original island, unlike metastasis to different organs. As a result, spatial dissemination of rats is less associated with differential treatment resistance than cancer metastasis.

Opportunities for future research

Here we discuss potential research directions motivated by these interdisciplinary comparisons.

Heterogeneity engineering

A promising new cancer approach that combines aspects of invasive species studies and cancer genetics is “heterogeneity engineering,” which we define to describe engineering of population heterogeneity to induce desired growth behaviors. In the invasive species field this concept has been commonly considered for gene drives, which are CRISPR/cas9 constructs engineered into an organism’s DNA in order to propagate the construct through the population [24–26]. Gene drives are being proposed to introduce maladaptive genetic traits with the goal of population eradication. The CRISPR/cas9 elements enable the construct to duplicate itself into the homologous chromosome of its genomic locus, allowing it to rapidly spread in a sexually reproducing population. An early gene drive concept has been to include a sex-linked infertility gene within the construct, which has the effect of limiting population reproduction while still allowing the construct to propagate. Recently, safety concerns about single locus drives have led to consideration of time-dependent multi-component genotype engineering via gene drive “daisy chains” [27]. Analogous ideas have been less considered in the cancer field, but could have similar value, e.g. to create tumor populations that grow rapidly but have specified genetic weaknesses that can later be targeted; or to synchronize multiclonal and microenvironmental dynamics to enhance immunotherapy.

Although gene drives cannot be applied to cancer cells because of their lack of sexual reproduction, the broader concept of heterogeneity engineering may still be useful. For example, cancer adaptive therapy is a version of heterogeneity engineering without genome editing that treats a tumor as a mixture of two subpopulations. In cancer adaptive therapy, treatment is timed to target a fast-growing subpopulation and then re-applied when the fast-growing subpopulation re-expands. This is analogous to adaptive ecosystem management, which denotes regular monitoring and episodic ‘knockdown’ of the invasive population, used to control invasive mammalian pests [28]. The success of cancer adaptive therapy in recent clinical trials [29,30], as well as analogous subclonal dynamics in xenograft studies [31], shows how time-dependent control of intratumoral heterogeneity can be useful for treatment outcomes. This utility arises because the competitive behaviors among subclones enable manipulation of tumor growth. We hypothesize that it would be possible to combine genetic manipulation and adaptive therapy concepts by removing some tumor cells from a patient and then genetically engineering them to outcompete other cancer cells while minimizing their ability to evolve resistance. Such cells could then be re-inserted into the tumor to replace the extant tumor cells, followed by a hyper-effective drug treatment to kill the engineered cells. Although this scenario may seem complex, competitive population replacement has been successful in fecal transplant treatment of gut bacterial dysbiosis [32], and the replacement populations can still be susceptible to antibiotic treatment.

Adaptive therapy is just one realization of heterogeneity engineering, and there are likely to be more powerful systems of multiple interacting subpopulations whose dynamics could each be triggered by external agents. Sophisticated phenotypes for cancer suppression are potentially possible, e.g. in which tradeoffs between immune evasion and chemotherapy resistance are sharpened, or particular cancer subpopulations are favored in the presence of specific immune cell types. Heterogeneity engineering of cancer by CRISPR/cas9 may also

eventually be achievable directly in vivo for patients [33]. Cancer cell specificity will be a key issue, and this topic can benefit from recent discussions of how to achieve cas9 sequence specificity for invader-specific targeting in the invasive species literature [27]. Comprehensive targeting of every cancer cell will also be challenging, and therefore new strategies that take into account subclonal competition will likely need to be integrated.

Population scale issues in evolution of resistance

The effects of intratumoral population dynamics on resistance remain poorly understood, aside from early concepts such as larger populations providing more opportunities for resistance [34,35] and some tumors being more treatable after a bottleneck [36]. Because resistance is common in cancer but rare for rat eradications, comparing their population dynamics can provide insights. Typical tumor and rat populations differ in scale, but the Predator-Free New Zealand project [37] aims to remove all 10^8–10^9 rats from the country's 26 million hectares of land [21], a population size similar to the cells in an initially detectable neoplasm. Other recently developed cancer models cover sizes from a few cells (microfluidics [38]) to thousands of cells (organoids [39]) to billions of cells (xenografts [40]). These models enable comparisons to a range of rat population sizes, which could illuminate fundamental questions in cancer biology such as how the propensity for resistance is related to the size of the tumor. This relationship affects strategies for early detection and treatment. While this relationship can be studied empirically in cancer experimental systems, basic understanding may require mathematical modeling. Aspects related to cancer spatial dynamics can be difficult to investigate because of the challenge of tracking individual cells in vivo for long periods of time. Rats, on the other hand, can be individually tagged and monitored, and therefore mathematical models of rat spatial dynamics may benefit analogous models for cancer. Population scale comparisons to other systems may also be illuminating. For example, immunoediting is a resistance mechanism of cancer to T-cells [41], but it imposes a fitness cost that is not well quantified. Characterizations of immunoediting as a function of population size in microbial or viral infections [42] may help quantify the likelihood of immuno-resistance during cancer growth or under immunotherapy. Such quantifications of fitness cost could be used to design adaptive therapy strategies [43] for cancers containing immunotherapy-resistant subclones.

Big data approaches to the tumor microenvironment

Methods to quantify the environment are rapidly developing in both cancer and macroscopic ecological systems, enabling potent data mining approaches. In the Predator-Free New Zealand project, invasive rats are being studied across islands with diverse latitudinal, rural, and urban biomes through quantifications such as temperature, rainfall, species tracking, remote sensing [44], and metagenomic DNA sampling [45]. Analogously, cancers are now studied across diverse tissue types, and the local microenvironment is quantified through measures such as MRI, immunostaining, cell sorting, and expression profiling. In each system, these rich datasets can be mined to reveal relationships among environment variables and invader growth. For example, random forests have been used to predict rat population growth [15] and ecological databases [46] provide powerful resources for study by algorithmic approaches such as ensemble regression, classification trees, and association rule mining [47]. Development of big data approaches for cancer histopathology,

immunohistochemistry, and expression data is a burgeoning field [48,49]. These approaches provide a new way to answer the pressing question of what tumor microenvironmental features are important to response [50].

Recent efforts in both fields have focused on advances in data collection. In cancer, image collections from TCGA have recently become available and these have been mined to build classifiers for outputs such as mutation status [51] or cancer subtype [48]. While many hospitals have additional slide collections, these are not openly available -- greater sharing could have a profound effect on the field. In ecological systems, new eco-sensing data collection efforts are actively being developed to forecast biodiversity [52]. This is applicable but not limited to invasive species ecology. For example, neural networks have been applied to high resolution camera images to assist in the identification of biological features such as coral reefs [53], a problem analogous to the identification of tumor regions with specific phenotypes. Approaches to determine features predictive of outcome are actively being developed in both fields. Natural geographic variations (e.g. low altitude vs. high altitude) assist in this analysis for ecological studies, just as stromal and vascular features may be helpful in cancer studies. Such approaches may clarify the spatial scales at which treatment resistance occurs in tumors, and they will be increasingly important as new technologies such as spatial transcriptomics [54] and imaging mass cytometry [55] become prevalent.

Conclusion

Cancer and invasive mammalian species are, despite the differences in scale, essentially similar in their processes of invasion, growth, and treatment. Key distinctions include the higher success of invasive mammal eradication projects, the low genetic divergence between cancer and normal cells, the high genetic divergence among clades of similarly treatable mammals, the greater intrapopulation heterogeneity of cancers, and the closer link between genetics and environment in cancers.

Promising future directions suggested by these comparisons include: heterogeneity engineering, multi-scale systems comparisons of population dynamics, and adaptation of image data mining approaches from ecological studies to cancer. Inter-system comparisons may help clarify parameter ranges for which heterogeneity engineering approaches will be effective [56]. It is promising that there have been recent calls to expand clinical trial testing of cancer adaptive therapy and treatment-switching [57]. The results of such studies would be highly informative for development of two-population heterogeneity engineering and shed light on when higher order population engineering might be most necessary. In organismal ecology studies, population engineering is just a part of the broader topic of eco-engineering, which may include environmental control as well. Large scale imaging approaches at a variety of scales provide the raw data for selecting what environmental perturbations may be useful in concert with heterogeneity engineering, and the feature analysis techniques being developed for eco-sensing projects should be applicable to the cancer problem.

Our discussions here could be developed in many ways. Firstly, we have focused mainly on the analogy between mammalian island invaders and cancer. Some strengths of this analogy are the genomic similarities between invasive mammals and human cancer cells, as well as the fact that both systems are invasions into closed systems. Many other invasive species systems can provide further insights, though they lack that particular combination of strengths. Examples include island invasions by insects, invasions of pests into agricultural fields, and microbial invasions into the human body [58]. Secondly, these discussions have emphasized genetic measures, but epigenetic, tissue-level, or organismal-level phenotypes will all be important. Thirdly, the survival data we have presented do not account for cancer survival / eradication success without treatment (e.g. spontaneous remission or animals naturally dying out). Further data collection will be necessary to take this into account, as they are not available in DIISE or TCGA.

Despite these caveats and the seeming differences across fields, invasive mammal eradication in New Zealand and cancer cure have many congruences in genetic and ecological complexity, positioning them as valuable parallel systems for developing improved eradication approaches. We believe that comparative studies of these and other invasive systems have great potential for developing new cancer treatment paradigms, and we hope that these perspectives will encourage others to develop insights across interdisciplinary divides.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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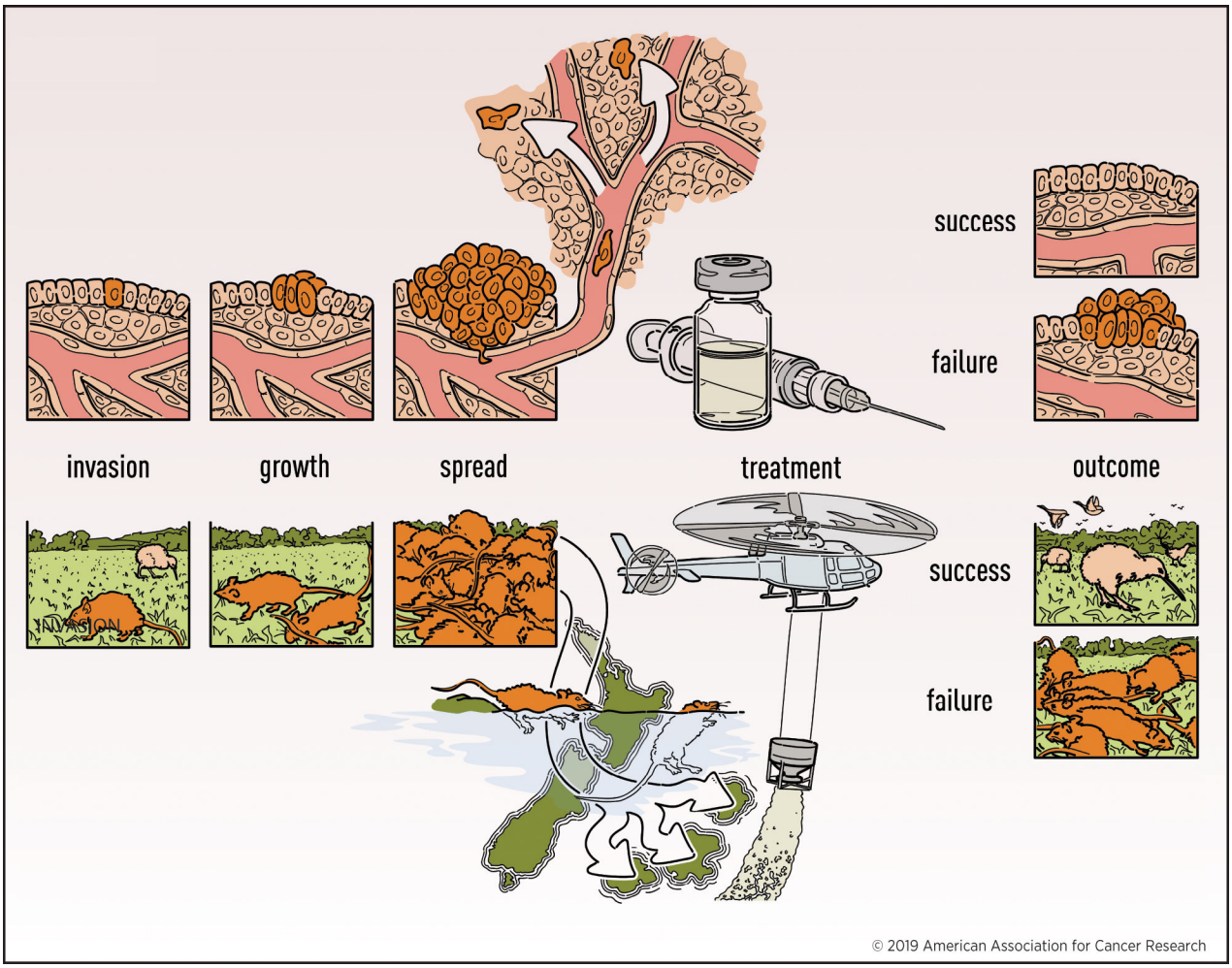

Fig 1. Comparison of invasive species and cancer.

Cancers and invasive species are systems with analogous processes for invasion, growth, spread, treatment, and outcome.

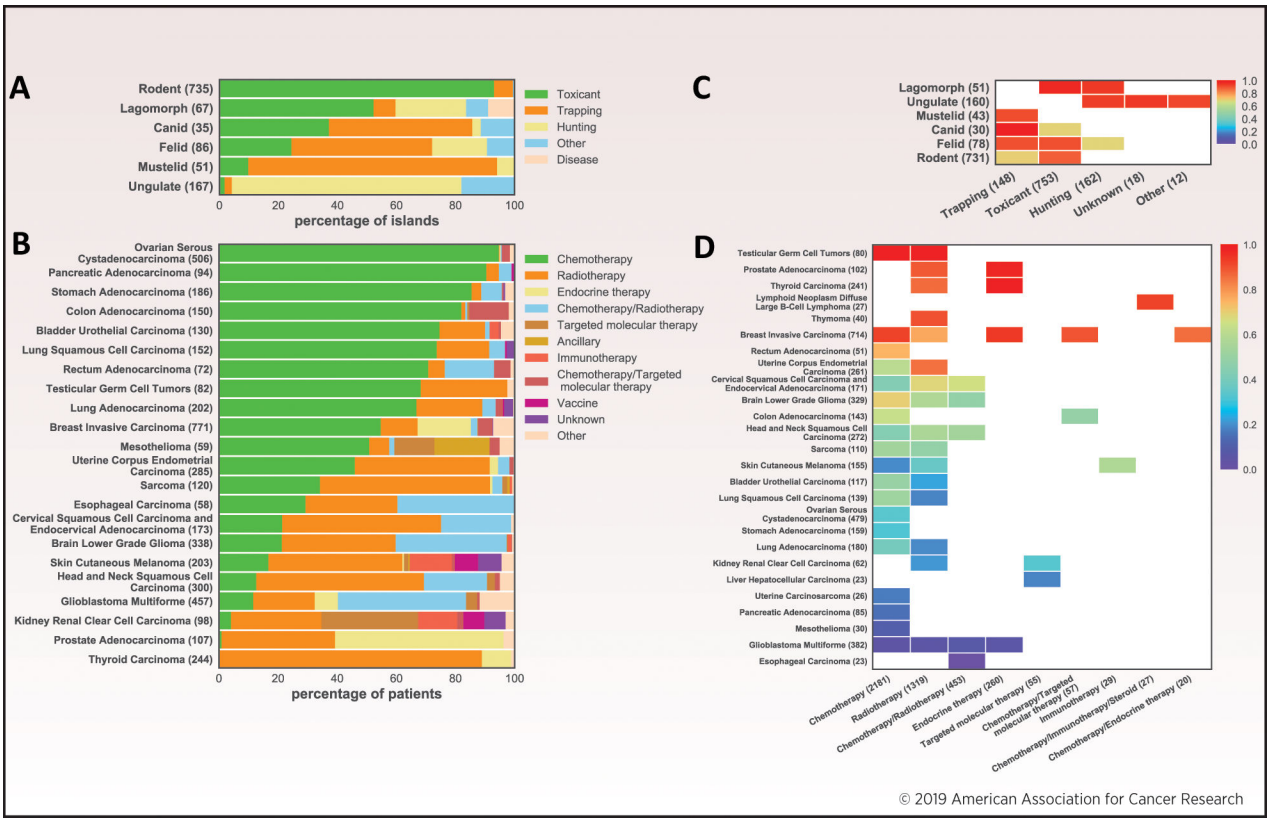

Fig 2. Prevalence of strategies for invasive species eradication and cancer treatment and their success rates.

(A) Percentage of islands that received specific primary eradication strategies, stratified by invasive mammalian species. **(B)** Percentage of patients that received specific initial treatments, stratified by cancer type. **(C)** Success rates for different primary treatments. Species are ordered by the mean of their success rates across all treatments. Only eradication cases with at least 10 islands were considered. **(D)** Five-year survival rate (Kaplan-Meier estimation) for cancer types as a function of initial treatment. Cancer types are ordered by the mean of their survival rates across all treatments. Data in panels (A) and (C) are from the Database of Island Invasive Species Eradications, with the number of islands in each dataset shown in parentheses. Data in panels (B) and (D) are from The Cancer Genome Atlas (TCGA) through TumorPortal [1], with the number of patients in each dataset shown in parentheses.

Table 1:

Comparison of key parallel factors for invasive mammalian species eradication and cancer treatment, and the relative impact of each factor on treatment success.

	Invasive mammals	**Cancer**	**Relative impact on treatment success**
Distinctiveness between host/invader	High: Millions of coding point mutations between invader and native species	Low: <1000 coding point mutations between tumor and normal cells	Lower treatment specificity and success against cancer than treatments against mammalian island invaders.
Genetic diversity among similarly treated species	Genetic differences are high: millions of coding mutations between different species.	Genetic differences are low: <100,000 coding germline differences between patients and <1000 coding mutations between patient tumor / germline.	Treatment response varies little between mammalian species but varies much between different cancer types.
Invader intrapopulation heterogeneity	Low: small populations (~10^3 for rats on most islands) and low mutation rates	High: large number of cells (~10^9) and high mutation rates	Cancers have more opportunities for evolution of resistance.
Invader environment interactions	Decoupling of invader genetics and ecological environment	Primary tumor genetics evolve in a fixed microenvironment, followed by decoupling at metastasis.	Microenvironment may be more targetable in cancer, especially for primary tumors. Rats are robust across island environments.