Computational Modeling of Ovarian Cancer Dynamics Suggests Optimal Strategies for Therapy and Screening

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Abstract

High-grade serous tubo-ovarian carcinoma (HGSC) is a major cause of cancer-related death. Treatment is not uniform with some patients undergoing primary debulking surgery followed by chemotherapy (PDS) and others being treated directly with chemotherapy and only having surgery after 3-4 cycles (NACT). Which strategy is optimal remains controversial. We developed a mathematical framework that simulates hierarchical or stochastic models of tumor initiation and reproduces clinical course of HGSC. After estimating parameter values, we infer that most patients harbor chemo-resistant HGSC cells at diagnosis, and that if the tumor burden is not too large and complete debulking can be achieved, PDS is superior to NACT due to better depletion of resistant cells. We further predict that earlier diagnosis of primary HGSC, followed by complete debulking, could improve survival, but its benefit in relapsed patients is likely to be limited. These predictions are supported by primary clinical data from multiple cohorts. Our results have clear implications for these key issues in HGSC management.

Significance Statement

The optimal timing of surgery / chemotherapy and the benefits of earlier diagnosis of HGSC remain controversial. We developed a mathematical framework of tumor dynamics, populated the model with primary clinical data, and reliably recapitulated clinical observations. Our model predicts that: (1) PDS is superior to NACT with relatively small tumor burden and when complete debulking is feasible; (2) timely adjuvant chemotherapy is critical for the outcome of PDS with <1 mm residual tumors; (3) earlier detection of relapse is unlikely beneficial with current therapies; (4) earlier detection of primary HGSC could have substantial benefit. These results provide insights into the evolutionary dynamics of HGSC, argue for new clinical trials to optimize therapy, and are potentially applicable to other tumor types.

Introduction

Ovarian cancer is the 8th most common cancer and cancer death in women worldwide[1]. High-grade serous tubo-ovarian cancer (HGSC) constitutes ~70% of all ovarian malignancies and has the worst prognosis[2]. Current treatment of most patients with HGSC consists of cytoreductive surgery and combination chemotherapy with platinum-containing DNA-crosslinking drugs and taxane-based microtubule-stabilizing agents[2]. Although treatment significantly improves survival, most women relapse with chemotherapy-refractory disease and eventually succumb[3]. Multiple mechanisms of chemo-resistance have been documented[4,5], including reduced intracellular drug accumulation[6], detoxification by increased levels of glutathione[7], altered DNA damage repair[8,9], dysfunctional apoptotic pathways[10,11], and hyper-activation of various cell signaling pathways[12–14]. These mechanistic studies are consistent with recent genomic analyses that reveal marked clonal evolution of HGSC during therapy[15]. Other evidence, however, supports a hierarchical organization of HGSC, featuring intrinsically chemo-resistant "cancer stem cells" (CSC) that can escape initial treatment and seed recurrence[16–18].

Although there is uniform agreement that HGSC patients should receive surgery and chemotherapy, the optimal order and timing of these modalities remain controversial. Two main options exist: primary debulking surgery with adjuvant chemotherapy (PDS), or neo-adjuvant chemotherapy, followed by interval debulking surgery (NACT)[19–24]. In either case, the surgical standard of care is to seek maximal cytoreduction, with the objective being to leave no visible residual disease. However, the precise definition of such "optimal debulking" can vary among different centers, surgeons, and reports[19,21,24,25].

Several studies have found similar outcomes after PDS or NACT, including two highly influential randomized trials (EORTC and CHORUS) carried out across multiple countries[22,23,26–28]. In both trials, however, the question of potential bias in patient recruitment has been raised, favoring potentially those with more extensive disease, who are less likely benefit from "upfront" surgery[23,28]. Consistent with this interpretation, overall survival in these trials was significantly shorter than that seen in other HGSC cohorts[19,24,29,30]. Closer examination of these reports reveals additional factors that might have influenced their conclusions. The EORTC study had inconsistencies in optimal debulking rates between participating centers, with the PDS-associated complete debulking data highly influenced by the results from a single institution[23]. The CHORUS study involved 76 clinical sites, and there were substantial differences in surgery execution and chemotherapy drug selection/dosage between them[28].

At Princess Margaret Cancer Center, retrospective data showed that PDS patients with no visible disease post-resection survived substantially longer (7-year survival >60%) than those receiving NACT (7-year survival ~10%). Furthermore, although residual tumor post-resection is a critical determinant of survival, its influence on the PDS group was far more dramatic than on NACT group[24]. Of course, this report suffers from deficiencies common to all retrospective analyses, including lack of randomization to account for tumor burden at diagnosis and other factors; indeed, the NACT group in this study did have more extensive disease.

Another controversy in HGSC management focuses on the potential benefit of earlier diagnosis. Earlier diagnosis of primary HGSC is generally assumed to enhance patient survival and quality of life[3]. Intuitively, one might predict that the same reasoning would apply to recurrent disease; however, survival is similar in relapsed patients treated earlier, based on increasing serum CA125 levels, than in those treated only when physical symptoms of recurrence appear[31]. Conceivably, the lead time between CA125 rise and clinical recurrence is too short for earlier chemotherapy to be beneficial; if so, then patient survival might be extended by more sensitive methods, such as testing for circulating tumor DNA (ctDNA)[32,33].

To address these issues, we developed a mathematical framework that models the dynamics of HGSC progression, response to surgery and chemotherapy, and recurrence. Our results, generated over a wide range of parameters and accounting for hierarchical and stochastic models of tumor initiation, argue that PDS is superior to NACT when complete debulking is feasible and suggest that with currently available therapies, the benefits of earlier detection are intrinsically restricted to primary HGSC.

Results

Clinical Cohorts

To train and evaluate our model, we used two independent cohorts, comprising a total of 285 FIGO Stage IIIC-IV HGSC patients (Table 1 and SI Appendix Fig. S1). The first dataset contains information on 148 patients who were treated by PDS or NACT at University Health Network (UHN) between March 2003 and November 2011[24]. In this cohort, “complete debulking” (no visible disease, operationally defined here as <1 mm residual tumor) was achieved in 97 patients, whereas 51 patients had 1-10 mm of residual tumor. Among the 97 patients with complete debulking, 40 received upfront surgery, followed by 6 cycles of platinum and taxane-based chemotherapy (hereafter, “PDS <1 mm”), whereas the other 57 patients were treated with upfront chemotherapy, followed by interval surgery after the first 3-4 cycles (hereafter, “NACT <1 mm”). For each patient, descriptions of tumor size post-surgery and serum CA125 levels over the course of treatment were recorded (Fig. 1a). As reported previously[24], overall survival was much better for patients in the PDS <1 mm group (Fig. 1b). However, patients in the NACT <1 mm group tended to have greater tumor burden at diagnosis[24], confounding direct comparison of the survival curves. Data from these patients (termed “Training Set” below) were used to train the parameters in our computational model.

The other 51 patients in the UHN dataset underwent debulking but were left with residual tumor of 1-10 mm in diameter. Lack of complete gross debulking usually was due to tumor location. As reported previously[24], there was a significant negative association between residual tumor size and patient survival in patients who had undergone PDS (Fig. 1c), but no association was found in the NACT group (Fig. 1d). Similar trends have been observed in several other studies investigating the association between patient survival and residual tumor size[19,20,34]. Independent of the <1 mm cohort, we used this 1-10 mm cohort ("Validation Set 1", below) in initial tests of the validity of our computational model (SI Appendix, Fig. S1).

The second dataset, which is independent of the UHN cohort, contains information on 137 patients diagnosed from October 2001 to June 2005 and enrolled in the CAN-CCTG-OV16 trial (hereafter, "CCTG cohort"). These patients all received upfront surgery, followed by 8 cycles of carboplatin/paclitaxel chemotherapy. The median delay for chemotherapy after surgery was 0.8 month (compared with 1 month at UHN). In 20 patients, debulking to <1 mm residual tumor was achieved, 36 patients had 1-10 mm residual tumor, and 81 patients had residual tumor diameter >10 mm. Data from the CCTG cohort was used to further evaluate the validity of our computational model (SI Appendix, Fig. S1).

Model Overview

We developed a mathematical model of cancer initiation and evolution to investigate the dynamics of HGSC growth, the onset of chemo-resistance, and the effects of various treatment strategies on patient survival (Fig. 1e and detailed in the SI Appendix Methods section). Our initial framework was based on work by the Michor laboratory[35,36] and considers exponential expansion of HGSC cells starting from a single cancer cell that has all of the genetic alterations needed for proliferation and metastasis, but has not developed chemo-resistance. This framework assumes that during tumor development/progression, any chemo-sensitive HGSC cell can acquire mutations and/or epigenetic alterations that enable chemo-resistance; i.e., it assumes a stochastic model of tumor initiation. However, the model can be modified to accommodate a hierarchical organization of HGSC, in which a relatively chemo-resistant CSC gives rise to chemo-sensitive progeny. Importantly, the predictions/implications of the hierarchical and stochastic models are essentially the same (see below, Materials and Methods, and Supplemental Information for more details).

Estimation of Parameter Values

For most model parameters, a clinically relevant range of values could be deduced from clinical data or previous publications (see Methods section for detailed description of parameter value estimations). We then varied u (the probability of conversion of a chemo-sensitive cell to a chemo-resistant cell in each cell division) and ε (the proportion of cancer cells outside the peritoneum and unresectable) over a wide range and computed the expected distribution of survival of patients by Monte-Carlo simulation. We compared the deviation between the Training Set data and the predictions of our model for each combination of u and ε, and from the region of best fit for these parameters, we inferred that $10^{-9} < u < 10^{-7}$ and $10^{-9} < \varepsilon < 10^{-5}$ (Fig. 2a). Finer investigation of the fit between data and theory in this parameter region showed that $u = 10^{-7.6}$ and $\varepsilon = 10^{-7.4}$ is the best combination of these parameters, as it minimizes the deviation between data and theory (Fig. 2b). Importantly, the trained value for u is consistent with chemo-resistant conversion rates estimated for multiple other cancers[37–40]. The trained value for ε predicts that inaccessible cancer cells outside the peritoneum are less numerous than cancer cells inside the peritoneum after first-line therapy, which comports with clinical observations that recurrent HGSC occurs predominantly inside the abdominal cavity. Using the trained parameter values, we compared the observed (Fig. 1b) and predicted (Fig. 2c) distributions of patient survival in the Training Set. Reassuringly, the model predictions closely recapitulated the clinical observations (Fig.s 2d-e). Although this combination of u and ε yielded the best prediction using training set data, and big deviations from these values led to worse predictions (SI Appendix, Fig. S2a-b), adjusting their values over a smaller range did not lead to substantial decrease in prediction accuracy (SI Appendix, Fig. S2c). Therefore, in our follow-up analyses, in addition to using the base values of $u = 10^{-7.6}$ and $\varepsilon = 10^{-7.4}$, we also tried alternative combinations to test the robustness of our model predictions.

Using our mathematical framework and these estimated rates, we then calculated the probability (as a function of tumor burden) that chemo-resistant cells are present at diagnosis (SI Appendix, Fig. S3a). Consistent with clinical and theoretical studies of other malignancies[37–39,41–45], our model predicted that at least some chemo-resistant cells are always present at the start of therapy for HGSC. We varied the values for each model parameter over a large range to test their influence on the calculated number of resistant cells at diagnosis: within the ranges tested, this number almost always exceeds 10^3 (Fig.s S3b-g).

Model Validation

To assess the accuracy of our mathematical framework and the validity of the estimated parameter values, we analyzed the model-predicted distribution of overall survival using data from several test sets (Fig. 3). First, we predicted the survival of patients in Validation Set 1 (Fig.s 3a-b), by adjusting the value of M (the number of cancer cells left in the peritoneum after surgery), which can be approximated from the operative notes (categorized as "<1mm", "1-10mm", or ">10mm"). Comparison of the observed (Fig. 3a) and predicted (Fig. 3b) distributions of patient survival revealed no significant differences (Fig.s 3c-d).

The data for the above validation exercise were derived from different patients than those used for the Training Set, but both cohorts were treated over the same time period at the same institution (UHN). To more rigorously test the validity of our model, we analyzed independent patient data, derived from the CCTG cohort. As noted above, the treatment course of these patients also differed somewhat from that of the UHN patients, enabling an even better test of the general applicability of our framework. We incorporated these differences into the model and predicted the survival of patients in the CCTG trial. Again, the model predictions fit very well with clinical observations, and recapitulated the theme that PDS with minimal residual tumor results in the best outcome (Fig.s 3e-i).

Predicted Outcome of PDS and NACT in Patients with Identical Tumor Burden

Confident in the predictive power of our mathematical framework, we modeled the expected clinical outcome of PDS and NACT in patients with the same initial tumor burden by imposing the same distribution of M_1 on both groups. Our model predicts that PDS patients should survive longer than NACT patients when controlled for residual post-surgery tumor mass. As residual tumor increases, however, the predicted survival advantage of PDS shrinks (Fig.s 4a-b). To investigate the underlying reason(s) for these predictions, we explored the predicted dynamics of chemo-sensitive (blue) and chemo-resistant (green) HGSC cells in patients undergoing treatment by PDS or NACT (Fig.s 4c-d). Our model predicts that, at diagnosis, a typical HGSC patient has low numbers of chemo-resistant cells. In women who undergo PDS, debulking surgery (S in Fig. 4c) dramatically reduces the number of chemo-sensitive and chemo-resistant cancer cells, because these cells appear identical to the surgeon and therefore have an equal likelihood of removal. Depending on the (stochastic) distribution of chemo-resistant cells within the abdominal cavity of the HGSC patient, all chemo-resistant cells present at diagnosis might have been eliminated by complete debulking, with the residual chemo-resistant cell number following a Poisson distribution. Follow-up chemotherapy (C in Fig. 4c) can then reduce the remaining chemo-sensitive cells to very low numbers or even eradicate them.

By contrast, with NACT, neo-adjuvant chemotherapy (C) dramatically enriches for chemo-resistant cells while killing the sensitive cells; consequently, chemo-resistant cells comprise a large proportion of total tumor cells at surgery (S). Because chemo-sensitive cells are largely depleted by the neo-adjuvant chemotherapy, the amount of residual tumor visible to the surgeon is reduced substantially. Consequently, it is virtually impossible for interval debulking surgery to fully deplete the chemo-resistant cells (Fig. 4d). We propose that this relative inability of NACT to deplete chemo-resistant cells explains the difference in outcome from patients treated with PDS. Importantly, this conclusion is based on intrinsic properties of the dynamics of cancer proliferation, survival, and death.

We then explored why the predicted superiority of PDS over NACT depends on residual tumor burden post-surgery. By examining the expected distribution of chemo-sensitive and -resistant cell numbers after first-line therapy, we found that PDS with <1 mm residual tumor potentially can deplete all cancer cells in a significant proportion of HGSC patients (Fig. 4e). This finding can account for the considerable survival difference between PDS and NACT with <1 mm residual tumor. By contrast, with >1 mm residual tumor, neither PDS nor NACT depletes all malignant cells, even though fewer tumor cells are predicted to remain after PDS (Fig. 4f). Consequently, almost all patients with >1 mm residual tumor are predicted to relapse and eventually die because of the inability of current agents to kill chemo-resistant cells. This analysis explains why PDS can be superior to NACT when complete debulking is achieved and why residual tumor mass is a key determinant of survival after PDS but not NACT (Fig.s 3a-b). Our predictions regarding PDS vs NACT are illustrated in Fig. 4g.

Test the robustness and generalizability of model prediction

To test the robustness of our predictions and quantitatively examine the influence of each factor on survival, we varied each parameter in our model over a large range. We identified multiple factors that influence the magnitude of the predicted difference between PDS and NACT (SI Appendix, Fig. S4). For example, faster growth of cancer cells does not necessarily imply worse survival. Specifically, although elevated growth rate of chemo-resistant cells in the absence of chemotherapy leads to worse survival, faster-growing, chemo-sensitive cells can sometimes result in better survival (Fig.s S4a-d). This result can be attributed to a lower percentage of chemo-resistant cells at diagnosis when chemo-sensitive cells proliferate faster. However, if the proliferation rate of chemo-sensitive cells is too high (e.g., when $r = 3$), new chemo-resistant cells might be generated between the time of surgery and adjuvant chemotherapy, resulting in worse survival (SI Appendix, Fig. S4a). We also inferred that the relative importance of chemo-sensitive and chemo-resistant cells in influencing survival might differ at different stages along the clinical course. During treatment-free periods, the growth rate of chemo-resistant cells could play a more dominant role in influencing patient survival (Fig.s S4a-d), because they underlie ultimate treatment failure. However, during periods of chemotherapy, the growth rate (or depletion rate) of chemo-sensitive cells might play a more dominant role (Fig.s S4e-h), because the depletion rate of chemo-sensitive cells at this stage determines whether they can be completely eradicated by chemotherapy. By contrast, chemo-resistant cells likely will endure. As a result, drug choice and dose, which likely influences the efficiency of elimination of chemo-sensitive cells, is predicted to be a critical factor in treatment outcome. Some molecular subgroups of HGSC (e.g., *CCNE1*-amplified tumors) are highly resistant to current chemotherapy. Our model predicts that these patients would be refractory to PDS, even if complete debulking is achieved (Fig.s S4e-f, when r' is high or d' is low). Residual cancer cell abundance after tumor resection can dramatically influence patient survival, especially in the PDS group (SI Appendix, Fig. S4i), suggesting that primary cytoreductive surgery should aim for complete removal of cancer cells even though chemotherapy will usually follow. Tumor size at diagnosis can be a critical factor determining whether a patient can be cured (SI Appendix, Fig. S4j) and is addressed below. By contrast, varying the parameter value of tumor size at patient death did not influence the length of survival (SI Appendix, Fig. S4k).

To further test the general applicability of our model, we asked whether it could explain the similar outcome of patients treated with PDS and NACT in prospective clinical studies, such as the CHORUS trial[28], using their patient data. Overall, patients in this study had substantially shorter survival than cohorts in most other studies. We reasoned that this might be attributable to more severe disease at diagnosis in patients in this cohort, such as higher tumor burden and/or more severe systemic metastasis. We therefore re-trained the parameters M_1 and ε for patients in the CHORUS study, only using the data from PDS or NACT 1-10 mm groups in this cohort. Indeed, the model predicted higher values for both parameters (median of $M_1 = 10^{12.2}$ and $\varepsilon = 10^{-2.9}$) (SI Appendix, Fig. S5a). When we then use these parameter values to predict the survival of PDS and NACT <1 mm groups, the model predicted no significant difference between the two regimens, consistent with the trend published in the original study[28] (SI Appendix, Fig. S5b). These results indicate that the contradiction between existing retrospective studies and prospective trials might have derived from differences in disease severity at diagnosis of patients in each cohort. This analysis further supports the conclusion that disease burden information is a critical factor in choosing PDS or NACT. Importantly, our prediction is corroborated by a recent pooled analysis of the CHORUS and EORTC trials, which showed that PDS tends to outperform NACT in patients with stage IIIC but not stage IV disease[46].

We also considered two alternative scenarios: (1) that heterogeneous populations of (variably) chemo-resistant cells exist in the same patient (Fig.s S6a-c), or (2) that HGSC initiates from an intrinsically chemo-resistant “cancer stem cell”, which differentiates into chemo-sensitive “tumor progenitor cells” (Fig.s S6d-f). Either of these assumptions results in the same conclusions as the original model.

Modeling Alternative Treatment Regimens

We next utilized our model to predict the effects of altering current treatment regimens on patient outcomes. For both PDS and NACT, adjuvant chemotherapy typically begins 4-5 weeks post-surgery, an interval chosen to allow patients to recover from their typically aggressive surgical treatment. The length of the post-surgical chemotherapy delay varies between centers and among physicians, but its influence on treatment outcome has not been studied carefully. We varied the length of treatment delay in our model and tested the predicted effects on patient survival. For PDS with <1 mm residual tumor, earlier initiation of chemotherapy might prolong survival, whereas longer treatment delay might worsen outcome (Fig. 5a, $p<0.0001$). For PDS with >1 mm residual tumor or for NACT with any amount of residual tumor, treatment delay (within the same range) is predicted to have little effect on outcome (Fig.s 5b-d). These differences arise primarily because upfront surgery that results in <1 mm residual tumor, followed by chemotherapy, potentially can deplete all tumor cells when treatment delay is minimized (Fig. 5e). The probability of depletion decreases with longer delay, largely because chemo-resistant cells can arise during the gap between upfront surgery and adjuvant chemotherapy (Fig. 5e). By contrast, PDS with >1 mm residual tumor or NACT is unlikely to deplete all cancer cells (Fig.s S7a-c), irrespective of treatment delay. Our predictions on the critical nature of the interval between optimal debulking surgery and adjuvant chemotherapy are schematized in Fig. 5f.

Our model predicts that neo-adjuvant chemotherapy enriches for chemo-resistant cells and thus increases the percentage of chemo-resistant tumor cells remaining post-surgery in patients treated with NACT. Conceivably, reducing the number of cycles of neo-adjuvant chemotherapy might attenuate the enrichment for chemo-resistant cells, and if the same number of residual cancer cells remain after surgery, less neo-adjuvant chemotherapy might prolong survival. Indeed, our model predicts that patients undergoing NACT with <1 mm or >1 mm residual tumor could benefit slightly from reducing the number of pre-surgery chemotherapy cycles (Fig.s S7d-e). The small predicted improvement arises primarily because of more efficient reduction of the number of chemo-resistant cells at surgery. The benefit is limited, however, because for most patients, chemo-resistant cells are still unlikely to be eradicated after their enrichment during the neo-adjuvant chemotherapy period (Fig.s S7f-g).

Predicted Effects of Earlier Diagnosis on Survival

We also utilized our model to evaluate the potential benefits of earlier diagnosis. We first modeled the effects of diagnosing relapsed HGSC at the earliest possible time enabled by the currently used clinical test, CA-125 detection[47]. Contrary to the intuitive notion that earlier diagnosis of recurrence should be advantageous, we find that CA-125-based earlier diagnosis is not expected to improve survival (Fig.s 6a-b, red curves). We also asked if detecting recurrence earlier than is possible with CA-125 monitoring would be advantageous. Yet even with a sensitivity ~10^4 greater than that required for physical symptoms to appear (lead time >5 months), the current upper limit of sensitivity for ctDNA-based diagnosis of ovarian cancer[33], our model predicts no advantage in patient survival if recurrence is detected earlier (Fig.s 6a-b, green curves).

We explored the reason for this lack of survival advantage by modeling the theoretical numbers of chemo-sensitive and –resistant cells in a virtual patient whose recurrence is diagnosed with increasing levels of sensitivity (Fig. 6c). Although earlier diagnosis, followed by prompt re-institution of chemotherapy, can better deplete chemo-sensitive cells, it barely affects the chemo-resistant cells that have been enriched by first-line therapy, which ultimately expand and cause patient death. Therefore, earlier diagnosis is unlikely to improve survival when applied to relapsed cancers treated with standard cytotoxic chemotherapy regimens. Based on this result, we asked if treating relapsed tumors using a hypothetical drug with similar efficacy but a distinct resistance mechanism from platinum/paclitaxel would potentiate the benefit of earlier diagnosis of relapsed HGSC. Indeed, our model predicts that earlier diagnosis of relapsed cancer can be beneficial, but only with alternative second-line therapy (Fig. 6d-e). The magnitude of the advantage of earlier diagnosis of relapse primarily depends on the probability that earlier, but not later, intervention at relapse can be curative. Our predictions on the impact of earlier detection of relapsed tumor are illustrated in Fig. 6f.

Finally, we used our model to explore the potential benefit of earlier detection of treatment-naïve tumors. As HGSC deposits usually get larger and/or more disseminated if left untreated, earlier upfront diagnosis would likely identify smaller, probably less disseminated, tumors, potentially increasing the chances of complete debulking. We therefore focused our comparison on the predicted effects in patients with <1 mm residual tumor. Our analysis argues that earlier diagnosis of treatment-naïve cancer, with concomitant prompt intervention, can improve patient survival compared to regular diagnosis when controlled for residual cancer cell number post-surgery (SI Appendix, Fig.

S8). For PDS with complete debulking, the predicted survival benefit can be dramatic, primarily because lower volume and less diffuse tumor at presentation can increase the likelihood of disease eradication (Fig.s S8a, S8c, and S8e). By contrast, for NACT with complete debulking, the predicted benefit is rather limited, and the difference is detectable only if lead time is sufficient (Fig.s S8b, S8d, and S8f). In that case, chemo-resistant cells might not yet have arisen, and chemotherapy alone might be sufficient to eradicate disease.

Discussion

Mathematical modeling has demonstrated potential in the systematic and quantitative assessment of various treatments[44,48,49]. If the outcomes of different strategies could be modeled accurately *a priori*, clinical trials could focus on therapeutic combinations that are most likely to succeed, and improvements in patient outcomes could be accelerated. The potential benefits of modeling are particularly important for diseases with relatively limited patient populations, in which it is not possible to do multiple clinical trials in parallel. Predictive models also can suggest when specific clinical controversies merit re-examination in the controlled trial setting. Our mathematical model of HGSC defines factors that affect the evolution of chemotherapy resistance and can predict patient survival based on the growth dynamics of chemo-sensitive and –resistant cells, whether stochastic or hierarchical models of tumor initiation are assumed. Our results have important implications for HGSC therapy and screening.

We populated our model with clinical data from ~300 patients receiving PDS or NACT. After estimating the rates of tumor cell proliferation and conversion to chemo-resistance, we concluded that most HGSC patients probably harbor chemo-resistant cancer cells at diagnosis. Our outcome predictions closely match patient data from multiple sources and support clinical observations that: (1) PDS that leaves minimal residual tumor is the optimal treatment strategy for patients who can tolerate the surgery and who do not have overwhelming or inaccessible disease burden at presentation; (2) residual tumor size is a critical determinant of survival in patients undergoing PDS, but not NACT; (3) earlier diagnosis of relapsed cancer does not – and cannot – lead to better survival with current therapies; and (4) earlier diagnosis of primary (treatment-naïve) HGSC could dramatically improve outcomes from this devastating disease, if PDS with complete debulking is feasible.

Our model shows clearly that, for HGSC patients whose tumor burden at diagnosis is not too severe, PDS with complete debulking should lead to a better outcome than NACT with complete debulking. We infer that the reason for the superior predicted outcome of PDS is that upfront surgery can deplete minority chemo-resistant cells more effectively, leaving adjuvant chemotherapy to eradicate residual chemo-sensitive cells. If debulking surgery removes all chemo-resistant cells, the PDS regimen can be curative. By contrast, cure is unlikely after NACT for at least two reasons. First, neo-adjuvant chemotherapy enriches for, and allows the continued expansion of, chemo-resistant cells. Second, by depleting bulk chemo-sensitive cells, chemotherapy removes tumor mass that can mark the location of chemo-resistant cells interspersed in metastatic deposits. We suggest that removing these "sentinel" chemo-sensitive cells renders interval surgery less effective than upfront surgery in depleting chemo-resistant cells, which are the cells that eventually cause death. At present, the most feasible way to achieve this goal is by surgically removing such cells, which is much more likely with the PDS regime. Of course, the development of drugs that can target these resistant cells should alter these conclusions[17,22,50].

Previous clinical studies differed over whether PDS or NACT is superior. A retrospective analysis of patients treated between 1980 and 1997 found no difference in outcome between PDS and NACT[26]. By contrast, several meta-analyses indicated that

NACT is associated with worse prognosis[21,51]. This controversy occasioned two large, controlled clinical trials to compare PDS and NACT[23,28], which found no significant difference in patient survival between PDS and NACT. A major reason for these contradictions can be attributed to differences in study design and patient selection. Our model shows how these contradictions can be reconciled. For the retrospective studies, where patients underwent less pre-selection and thus are more likely to represent the bulk population, our model predicts that PDS should be superior to NACT with complete debulking. In the prospective studies, only patients with "extensive" HGSC were recruited, which might explain the notably worse outcome of patients in this study, especially in PDS <1 mm group, compared with multiple other reports[19,20,24,52]. Our computational model predicts that elevated upfront tumor burden should lead to worse overall survival and obscure the difference in outcome between PDS and NACT, even when complete debulking is performed (SI Appendix, Fig. S4j, Fig. S5). In particular, differences in the magnitude of ε, the "inaccessible proportion", alone might contribute to the lack of difference between PDS and NACT in these trials. This prediction is corroborated by a recent pooled analysis of the EORTC and CHORUS trials[46]. Our results also imply that knowing the feasibility of complete debulking before surgery could assist in choosing PDS vs NACT for treatment. Indeed, several studies reported that laparoscopy can be used for this purpose[53–55].

An earlier mathematical modeling study, based on a Gompertzian growth model, argued that NACT should be superior to PDS[56]. However, that study did not account for the different dynamics of chemo-sensitive and –resistant cells and assumed equal efficiency of surgical depletion of large and small tumors, which ignores the intrinsic limitations of surgery. Such assumptions can lead to serious errors in modeling HGSC. For example, although aggressive surgery might reduce a tumor containing $>10^{11}$ cells to a mass of $<10^{7}$ cells, a tumor containing $<10^{6}$ cells is unlikely to be visible during surgery, making it highly unlikely that such a tumor can be surgically reduced to $<10^{2}$ cells.

A study of the optimal order of surgery and chemotherapy in pancreatic cancer concluded that neo-adjuvant chemotherapy should be superior to upfront surgery[36]. However, the biology and chemo-responsiveness of pancreatic cancer and HGSC differ substantially: whereas HGSC is usually quite chemo-responsive, pancreatic cancer is notoriously chemo-resistant. The differential influence on tumor visibility following chemotherapy likely underlies the different predictions in the two diseases. Nevertheless, the difference between our conclusions and those of Haeno *et al.* argue for caution in extrapolating their conclusions to other types of cancer.

Some treatment considerations are beyond the scope of computational modeling. For example, in many patients (e.g., the infirm), NACT is preferred simply because of the potential risks of this large operation, which include bowel perforation, uncontrolled bleeding and/or the stresses of prolonged surgery/anesthesia. In such scenarios, treatment choice depends primarily on technical feasibility. Another limitation of our model is that we do not simulate potential effects of the tumor microenvironment (TME), including infiltrating immune cells. Recent studies from our group and by others suggest that the immune microenvironment of HGSC, shaped by tumor-initiating mutations, has a major influence on HGSC biology[57,58]. The paucity of data on immune landscape characterization in clinical samples and our limited understanding of the tumor-infiltrating immune cells at present preclude accurate simulation of such effects. With the increasing availability of clinical data and better mechanistic understanding of cancer-immune interaction, TME effects could be integrated into our model in the future.

Our model also enables quantitative analysis of the dependence of treatment outcome on various factors under different scenarios, providing a powerful tool to assist clinical decision-making. For example, we found that the advantage of PDS over NACT diminishes with larger residual tumor post-surgery, more extensive metastases at unresectable locations, and/or a higher percentage of chemo-resistant cells at diagnosis (Fig.s 3a-b, and S4a-c). These features might help explain the similar overall survival between PDS and NACT groups in studies involving patients with more extensive upfront disease or less complete surgical removal[23,26]. Our analysis argues that for PDS patients with <1 mm residual tumor, adjuvant chemotherapy should start as early as possible to provide the best chance of curative outcome; indeed, we predict that differences of even a few weeks might dramatically alter the chance for curative outcome. Conversely, if complete debulking is not achieved at primary surgery, delaying chemotherapy is less likely to affect survival. These predictions are consistent with the results of a meta-analysis of clinical studies[59], which found that each extra week of delay was associated with a significantly decreased overall survival in patients with PDS <1 mm residual tumor, but not in patients with visible residual disease. We also predict that reducing the number of cycles of neo-adjuvant chemotherapy might result in slightly improved overall survival for NACT patients, a prediction that is consistent with a meta-analysis[51] and a very recent clinical study[60]. Recent work suggests that NACT alters the immune cells in the tumor to a more anti-tumor state and might prime the tumor to respond better to immunotherapy[61]. Therefore, we speculate that fewer cycles of neo-adjuvant chemo might enrich for chemo-resistant cells to a more limited extent, while also activating the immune response.

A final prediction of our model is that earlier diagnosis should have quite different impact on relapsed versus treatment-naïve patients. For the former, earlier diagnosis is unlikely to improve overall survival, primarily because earlier treatment of recurrent tumors with existing agents cannot deplete chemo-resistant cells that have been enriched over the clinical course. This prediction matches very well with earlier clinical observations[31]. Two scenarios might alter this conclusion: (1) if effective chemotherapy with a resistance profile orthogonal to platinum/taxane-based therapy were to become available at relapse; or (2) if effective debulking could be achieved at relapse. Effective drugs against HGSC remain a major clinical limitation[62,63]. PARP inhibitors, which are used as maintenance therapy following platinum-taxane therapy and especially effective in patients with homologous recombination deficiency[64], could serve as such alternative agents for relapsed cancer. If they have different resistance mechanisms from first-line therapy, our findings suggest employing such alternative agents as early as possible upon tumor relapse. Furthermore, the use of such alternative agents at relapse can be beneficial compared with re-using the first-line drugs, even in the absence of earlier diagnosis (Fig. 6e vs Fig. 6b). Similar proposals on combining drugs with orthogonal resistance profiles have been raised by others[37,65]. Surgery is not typically performed on recurrent HGSC, and its efficacy could be limited by the proportion of cancer cells at unresectable locations at disease relapse. Nevertheless, our model calls for re-evaluation of feasibility and potential efficacy of secondary surgery for the benefit of earlier diagnosis. Consistent with our analysis, retrospective studies[66,67] and a recent prospective trial[68] indicate that secondary surgery achieving complete debulking can be beneficial for HGSC patients with platinum-sensitive tumors.

By contrast, our model predicts that earlier diagnosis of treatment-naïve cancer could improve overall survival for at least two reasons: (1) chemo-resistant cells are usually not enriched prior to treatment and earlier intervention can reduce the likelihood that significant numbers of these cells will arise; and (2) earlier upfront surgery has a better chance of removing all chemo-resistant cells, assuming that tumor cells have not diffused throughout the peritoneal cavity or seeded unresectable locations. This trend is consistent with a recent clinical trial testing the benefit of earlier upfront diagnosis of HGSC. Although screening did not identify ovarian cancer at an earlier stage, women who were screened annually for serum CA125 levels had reduced mortality from ovarian cancer than those with no screening[69]. In that study, the survival improvement by CA125-based screening was significant but modest, and might be attributable to at least two factors: (1) the lead time of CA125-based screening is on average less than 1 year[70,71], which is shorter than the screening interval; (2) early-diagnosed patients may receive either PDS or NACT, and our model predicts that particularly in this setting, NACT might counteract the benefit of earlier diagnosis. Two additional potential advantages of earlier diagnosis and treatment of naïve HGSC are not explicitly considered in this analysis: (1) earlier diagnosis might increase the likelihood of complete debulking; and (2) patients considered treatable only by NACT with regular diagnosis might be eligible for PDS with earlier diagnosis.

In summary, our analyses suggest that future randomized clinical trials might consider (1) the influence of the interval between primary debulking surgery and adjuvant chemotherapy on treatment outcome, particularly for those with <1 mm residual disease, (2) the association between the number of neo-adjuvant chemotherapy cycles and treatment outcome, (3) the effects of alternative chemotherapy and/or complete secondary surgery on relapsed tumor, especially when coupled to earlier diagnosis, and (4) better ways to estimate tumor mass at presentation, and thereby refine the prediction of which patients are most likely to benefit from PDS. Our results also argue that whereas not all patients who can achieve complete cytoreduction will benefit from PDS over NACT (give the importance of, and difficulty in measuring, ε), a subset of patients exist whose only chance of long-term survival or cure is the former regime. Finally, the mathematical abstraction makes our framework potentially applicable to evaluating different treatment strategies in other malignancies.

Materials and Methods

Patient Information

Clinical data from 285 HGSC patients were obtained from patient records at University Health Network (148 patients) and from the Canadian Cancer Trials Group OV16 NCT00028743 trial (137 patients). Medical record information, including date of diagnosis, age of patient, timing of treatment, extent of residual disease in diameter (<1 mm, 1-10 mm, or >10 mm), CA125 levels along the treatment course, and survival data (updated in 2014 for UHN data and 2010 for CCTG data) were recorded. Institutional REB approval was obtained through University Health Network and a Data Sharing Agreement was concluded with Canadian Cancer Trials Group.

Variables Used in Mathematical Model

We denote the following variables for the development of mathematical modeling: r, division rate of chemo-sensitive cells in the absence of chemotherapy; d, death rate of chemo-sensitive cells in the absence of chemotherapy; a, division rate of chemo-resistant cells in the absence of chemotherapy; b, death rate of chemo-resistant cells in the absence of chemotherapy; r', division rate of chemo-sensitive cells in the presence of chemotherapy; d', death rate of chemo-sensitive cells in the presence of chemotherapy; a', division rate of chemo-resistant cells in the presence of chemotherapy; b', death rate of chemo-resistant cells in the presence of chemotherapy; M, the number of residual cancer cells in the peritoneal cavity after surgery; M_1, the total number of cancer cells at diagnosis; M_2, the total number of cancer cells at death; u, the probability of conversion of a chemo-sensitive cell to a chemo-resistant cell in each cell division; ε, the proportion of cancer cells outside the peritoneum and unresectable.

Estimation of Parameter Values

Unless otherwise specified, clinically relevant parameter values were estimated and set as follows:

In the absence of chemotherapy, the proliferation rate of chemo-sensitive cells (r) was obtained from the normal distribution with mean 2 and standard deviation 0.8, based on a clinical study interrogating the doubling time of ovarian cancer cells by BrdU labeling[72]. Another study compared cancer cell proliferation rates in platinum responders and non-responders by thymidine labeling, and found that responders had significantly higher labeling index than patients with stable or progressive disease[73]. This analysis is consistent with several other studies that also found chemo-sensitive cells with proliferation advantage in the absence of therapy[74,75]. Accordingly, we set the proliferation rate of chemo-resistant cells (a) to a normal distribution with mean 0.84 and standard deviation 0.42. Death rates (d and b) were set as 10% of proliferation rates (r and a) respectively, which is within physiologically relevant range; in any case, varying this ratio over a large range does not affect the main conclusions of this paper.

During chemotherapy, the proliferation rate of chemo-sensitive cells (r') was set to 10% of that of randomly growing cells (r); the death rate of chemo-sensitive cells (d') was set to a normal distribution with mean 4.9 and standard deviation 1. These values were set to match the clinical observation that chemo-responsive relapse occurs on average ~11 months after 6 cycles of chemotherapy, indicating that cytotoxic reduction of chemo-sensitive cells by 6 cycles of chemotherapy corresponds to ~11 months of proliferation. Our inference is consistent with published efficacy of chemotherapy in HGSC[25,76]. The proliferation rate of chemo-resistant cells during chemotherapy (*a'*) was set to the same as that during random growth (*a*); the death rate of chemo-resistant cells during chemotherapy (*b'*) was set to twice as that during randomly growing (*b*), or 20% of *a'*, to reflect a modest effect of chemotherapy on chemo-resistant cells. Conversion rate during chemotherapy (*u'*) was set as 10 times of that during randomly growing (*u*), to reflect the DNA-damaging effect of platinum-based chemotherapy.

The parameters reflecting cancer cell numbers (M, M_1, M_2) were obtained from normal distributions in base 10 logarithmic scale. The number of residual cancer cells immediately post-surgery (M) was set to mean 6 and standard deviation 0.4 on the log scale for <1 mm residual tumor, mean of 8 on the log scale for 1-10 mm residual cancer, and mean of 10 on the log scale for >10 mm residual cancer. The number of cancer cells at diagnosis (M_1) was initially set at different values in patients receiving PDS and NACT, to reflect the clinical observation that patients with NACT tend to have more extensive disease at diagnosis[24]. M_1 for PDS was set at mean 11.5 and standard deviation 0.4 on the log scale, and M_1 for NACT was set at mean 12 and standard deviation 0.4; these values result in NACT patients starting with >3x the cancer burden in the model than those receiving PDS. Moreover, we varied the ratio of tumor burden at diagnosis in NACT vs PDS patients from 1 to $10^{1.5}$, and the main conclusions hold over the entire range. M_2 was set to mean 13 and standard deviation 0.4 on the log scale.

We varied the values for all of the above parameters to test the robustness of our conclusions. We found that the main conclusions hold true, though the magnitude of the differences between PDS and NACT treatment outcomes may vary.

Mathematical Deduction of the Expected Number of Chemo-resistant Cells at Diagnosis

We deduced the expected the number of chemo-resistant cells at diagnosis based on previous studies[35,36]. We first calculated the probability that chemo-resistant cells exist at diagnosis (P_d), and then calculated the expected number of chemo-resistant cells at diagnosis (Y_d).

To calculate P_d, we summed the probabilities that the first successful lineage of chemo-resistant cells arises when there are 1, 2, 3, … M_l-1 chemo-sensitive cells. $P(x)$ denotes the probability that the first lineage arises when there are x chemo-sensitive cells. $P(x)$ can be expressed as the joint probability that no successful chemo-resistant lineage arises at 1, 2, 3, … x-1 chemo-sensitive cells, and that a successful lineage arises at exactly x chemo-sensitive cells. An expected $1/(1-d/r)$ divisions are needed for an effective increase of 1 chemo-sensitive cell, and during these divisions an expected $u/(1-d/r)$ chemo-resistant cells are generated, among which a proportion $(1-b/a)$ will successfully persist. Assuming that the number of surviving chemo-resistant cells generated by each division follows a Poisson distribution with mean $(1-b/a)u/(1-d/r)$[45], we derive $P(x)$:

$$P(x) = e^{-(x-1)\left(1-\frac{b}{a}\right)u/(1-\frac{d}{r})}\left(1-e^{-\left(1-\frac{b}{a}\right)u/(1-\frac{d}{r})}\right)$$

Thus, the probability that chemo-resistant cells exist at diagnosis, P_d, can be written as the sum of $P(x)$:

$$P_d = \sum_{x=1}^{M_1-1} e^{-\left(1-\frac{b}{a}\right)(x-1)u/\left(1-\frac{d}{r}\right)} \left(1 - e^{-\left(1-\frac{b}{a}\right)u/\left(1-\frac{d}{r}\right)}\right)$$

If we denote the time between the emergence of a successful chemo-resistant cell and diagnosis as τ_x, then the expected number of chemo-resistant cells at diagnosis in the patients who have them can be expressed as:

$$Y_d = \frac{1}{P_d} \sum_{x=1}^{M_1-1} e^{-\left(1-\frac{b}{a}\right)(x-1)u/\left(1-\frac{d}{r}\right)} \left(1 - e^{-\left(1-\frac{b}{a}\right)u/\left(1-\frac{d}{r}\right)}\right) e^{(a-b)\tau_x}$$

The amount of time τ_x satisfies:

$$x e^{(r-d)\tau_x} + e^{(a-b)\tau_x} = M_1$$

Simulation of the Dynamics of Cancer Cell Number after Diagnosis

As the numbers of chemo-sensitive (denoted by X) and –resistant (denoted by Y) cells at diagnosis are expected to be large, we approximated their dynamics after diagnosis with a deterministic model, simulating the effects of random growth, chemotherapy, and surgery (cancer cell numbers before and after surgery are denoted as X_{before}, Y_{before}, and X_{after}, Y_{after}, respectively):

Random growth:

$$\begin{cases} \frac{dX}{dt} = (r(1-u) - d)X \\ \frac{dY}{dt} = ruX + (a-b)Y \end{cases}$$

Chemotherapy:

$$\begin{cases} \frac{dX}{dt} = (r'(1-u') - d')X \\ \frac{dY}{dt} = r'u'X + (a'-b')Y \end{cases}$$

Surgery: $$\begin{cases} X_{after} = \frac{X_{before}}{X_{before}+Y_{before}} M + \varepsilon X_{before} \\ Y_{after} = \frac{Y_{before}}{X_{before}+Y_{before}} M + \varepsilon Y_{before} \end{cases}$$

Treatment is adjudged a "failure" if the number of cancer cells post-treatment exceeds that pre-treatment. In the case of treatment failure, our model simulates random growth of cancer cells to the total number of M_2, which marks patient death.

Estimation of Conversion Rate *u* and Unresectable Proportion ε

For each combination of candidate values for u and ε, we calculated the deviation of model prediction from clinical observations as:

$$Dev = \sqrt{\sum_i \left(death_{i-th\ year\ observed} - death_{i-th\ year\ predicted}\right)^2}$$

The combination that led to lowest deviation was used for model testing and further predictions.

Statistical Analyses

Comparisons of overall survival between 2 groups were performed by log-rank test. Comparisons of predicted survival between >3 groups were performed by log-rank test for trend when the order of groups is logical. Comparisons of distribution of overall survival between model predictions and clinical observations were performed by Chi-square test.

Author Contributions

S.G. and B.G.N. designed the study; S.G. constructed the computational model and performed the analyses; S.L., P.C., L.H., I.V., M.N., S.K., D.S.C., D.A.L., M.Q.B., B.R., and A.O. provided clinical expertise and critical therapeutic insights; A.S. provided computational and statistical expertise and helpful discussions; L.H. and I.V. extracted raw clinical data from UHN dataset; D.T. and W.R.P. extracted raw clinical data from CCTG dataset; M.B. and B.G.N. supervised the research. S.G. and B.G.N. wrote the manuscript.

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Competing Interests

D.S.C. reports reports personal fees from Bovie Medical Co. (now Apyx Medical), Verthermia Inc., C Surgeries, and Biom 'Up. He is also a former stock holder of Intuitive Surgical, Inc. and TransEnterix, Inc.

D.A.L has consulting/advisory role for Tesaro/GSK, Merck, receives research funding to institution from Merck, Tesaro, Clovis Oncology, Regeneron, Agenus, Takeda, Immunogen, VBL Therapeutics, Genentech, Celsion, Ambry, Splash Pharmaceuticals. He also is a founder of Nirova BioSense, Inc.

M.B. is a consultant to and receives sponsored research support from Novartis. MB is a consultant to and serves on the scientific advisory boards of Kronos Bio, H3 Biomedicine, and GV20 Oncotherapy.

B.G.N. is a co-founder, holds equity in, and received consulting fees from Navire Pharmaceuticals, Northern Biologics, Inc, and Jengu Therapeutics, Inc. He also is a member of the Scientific Advisory Board and receives consulting fees and equity from Avrinas, Inc., a member of the Scientific Advisory Board and has equity in Recursion Pharma, received consulting fees from MPM Capital, and was an expert witness for the Johnson and Johnson ovarian cancer talc litigation in US Federal Court. His spouse has or held equity in Amgen, Inc., Regeneron, Moderna, Inc., Gilead Sciences, Inc., and Arvinas, Inc.

Dr. Balkwill was on a scientific advisory board of the department in Toronto run by Dr. Oza in 2018. Dr. Balkwill and Dr. Levine are co-authors on a 2019 commentary article.

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Figure Legends

Fig. 1. Mathematical Framework of HGSC Clinical Course

(a) Representative CA125 levels during clinical course of a typical HGSC patient. Chemotherapy responsiveness decreases along the treatment course, indicating the accumulation of chemo-resistant cells.

(b-d) Kaplan-Meier survival curves for patients in the UHN dataset. Panel (b) compares the survival of patients with <1 mm residual tumor after treatment by PDS or NACT. Note that patients with PDS <1 mm lived significantly longer than those with NACT <1 mm ($p<0.0001$). Panel (c) compares the survival of patients treated by PDS with <1 mm versus 1-10 mm residual tumor. Note that patients with PDS <1 mm lived significantly longer than those with PDS 1-10 mm ($p<0.0001$). Panel (d) compares the survival of patients treated by NACT with <1 mm versus 1-10 mm residual tumor. Note that survival of these two groups was not significantly different ($p=0.46$).

(e) Mathematical framework for modeling HGSC progression. The model assumes the existence of chemo-sensitive and chemo-resistant HGSC cells. During random growth, chemo-sensitive cells divide at rate r, die at rate d, and convert into chemo-resistant cells with probability u per cell division; chemo-resistant cells divide at rate a and die at rate b. During chemotherapy, chemo-sensitive cells divide at rate r', die at rate d', and convert into chemo-resistant cells with probability u' per cell division; chemo-resistant cells divide at rate a' and die at rate b'. See text and Supplementary Experimental Procedures for details.

Fig. 2. Estimation of Parameter Values and Evaluation of Model Predictions

(a-b) Estimation of conversion rate (u) and inaccessible proportion (ε) in patients treated by PDS or NACT with <1 mm residual tumor, using data from the UHN cohort (Training Set). Colors represent the degree of deviation between clinical data and the predictions of the mathematical model. Lighter colors represent region of best fit between theory and observation. Panel (b) provides a finer scale analysis of the red dashed region in panel (a).

(c) Model prediction of survival of patients treated by PDS or NACT with <1 mm residual tumor. Parameter values are: $u = 10^{-7.6}$, $\varepsilon = 10^{-7.4}$, $d = r/10$, $b = a/10$, $a' = a$, $b' = a/5$, $u' = 10u$. Values for r, a, r', and d' were obtained from normal distributions. r was set with mean = 2 and s.d. = 0.8. a was set with mean = 0.84 and s.d. = 0.42. r' was set with mean = 0.2 and s.d. = 0.08. d' was set with mean = 4.9 and s.d. = 1. M_1, M_2, and M were obtained from normal distributions in the log-10 scale. $log_{10}M_1$ was set with mean = 11.5 and s.d. = 0.4 for PDS group and mean = 12 and s.d. = 0.4 for NACT group. $log_{10}M_2$ was set with mean = 13 and s.d. = 0.4. $log_{10}M$ was set with mean = 6 and s.d. = 0.4 for <1 mm residual cancer. (d-e) Comparisons of predicted and observed overall survival for PDS <1 mm (d) and NACT <1 mm (e) groups. There was no significant difference between the prediction and clinical data for (d) (p=0.20) or (e) (p=0.69).

Fig. 3. Evaluation of Model Predictions with Data from Validation Sets

(a-b) Observed (a) and predicted (b) overall survival of patients from the UHN dataset treated with PDS or NACT with 1-10 mm residual tumor.

(c-d) Comparison of predicted and observed survival for the PDS (c) and NACT (d) 1-10 mm residual tumor groups. There was no significant difference between the predictions and clinical data for either (c) (p=0.59) or (d) (p=0.21).

(e-f) Observed (e) and predicted (f) overall survival of patients in the CCTG cohort. Patients received PDS and had <1 mm, 1-10 mm, or >10 mm residual tumor.

(g-i) Predicted and observed survival of PDS-treated patients from the CCTG study with <1 mm (g), 1-10 mm (h), or >10 mm (i) residual tumor. There was no significant difference between predictions and clinical data for (g) (p=0.73), (h) (p=0.40), or (i) (p=0.42). Parameter values were the same as in Fig. 2c, except that $log_{10}M$ was set with mean = 8 and s.d. = 0.4 for the 1-10 mm residual group, and mean = 10 and s.d. = 0.4 for the >10 mm residual groups. Also, the gap between surgery and the start of chemotherapy was 1 month for the UHN patients and 0.8 month for the CCTG patients; UHN patients received 6 cycles of chemotherapy for first line PDS treatment, whereas CCTG patients received 8 cycles.

Fig. 4. Predicted Outcome of PDS and NACT Patients with Same Initial Tumor Burden

(a-b) Predicted survival of patients undergoing PDS (black curves) or NACT (red curves). All patients received 6 cycles of chemotherapy. Panel (a) shows the results for <1 mm residual tumor group, and panel (b) shows the result for 1-10 mm residual tumor group. Parameter values were as in Fig. 2c, except that $log_{10}M_1$ was set at the same value for the PDS and NACT groups, with mean = 11.5 and s.d. = 0.4.

(c-d) Simulation of representative progression dynamics for chemo-sensitive (green curves) and chemo-resistant (blue curves) cancer cells in a patient undergoing PDS (c) or NACT (d) treatment with optimal debulking. Treatment order is shown at the top of each plot; "S" indicates "surgery", and "C" indicates "chemotherapy".

(e-f) Distribution of number of chemo-sensitive and chemo-resistant cells for the PDS (black curves) and NACT (red curves) groups, with <1 mm (e) or 1-10 mm (f) residual tumor.

(g) Scheme illustrating HGSC clinical course following PDS or NACT treatment.

Fig. 5. Predicted Outcomes of Alternative Treatment Strategies

(a-d) Predicted survival of patients receiving PDS (a-b) or NACT (c-d) with different lengths of delay between debulking surgery and adjuvant chemotherapy. Panels (a) and (c) show expected results with <1 mm residual tumor after surgery; panels (b) and (d) show predicted results with 1-10 mm residual tumor.

(e) Distributions of the numbers of chemo-sensitive or -resistant cells after PDS (<1 mm residual tumor) with different intervals (colored lines) between debulking surgery and adjuvant chemotherapy.

(f) Scheme showing predicted HGSC clinical course following PDS (<1 mm residual tumor) with standard or delayed adjuvant chemotherapy.

Fig. 6. Predicted Effects of Earlier Diagnosis and Treatment of Relapsed Cancer

(a-b) Predicted survival of patients with relapsed cancer detected at different degrees of sensitivity. Predictions were stratified based on the first-line therapy performed, including

(a) PDS or (b) NACT with <1 mm residual tumor. "Standard" (black curves) represents diagnosis based on physical symptoms, when the number of cancer cells is comparable to M_1; "100x sensitivity" (red curves) and "10,000x sensitivity" (green curves) represent earlier treatment of recurrent disease with the number of cancer cells at diagnosis 1% or 0.01% that of M_1, respectively.

(c) Simulation of representative growth dynamics for chemo-sensitive (green curves) and chemo-resistant (blue curves) cancer cells in a patient treated by PDS with optimal debulking, with relapsed cancer diagnosed at different degrees of sensitivity. Earlier treatment of relapsed cancer can more effectively deplete chemo-sensitive cells but does not effectively change the trajectory of chemo-resistant cells, which are the ultimate cause of patient death. Parameter values are the same as in Fig. 2c.

(d-e) Predicted survival of patients with relapsed cancer detected at different degrees of sensitivity and treated with a different second-line chemotherapy. Predictions were stratified based on the first-line therapy performed, including (d) PDS or (e) NACT with <1 mm residual tumor. "Standard" (black curves) represents diagnosis based on physical symptoms, when the number of cancer cells is comparable to M_1; "100x sensitivity" (red curves) and "10,000x sensitivity" (green curves) represent earlier treatment of recurrent disease with the number of cancer cells at diagnosis 1% or 0.01% that of M_1, respectively.

(f) Scheme showing predicted clinical course of relapsed HGSC, with standard or earlier diagnosis at relapse.

TABLES

Table 1. Patient Characteristics in UHN and CCTG Cohorts

		UHN Cohort	CCTG Cohort
Total number of patients		148	137
Time of diagnosis*		2008 JAN (2005 OCT – 2009 MAR)	2003 NOV (2003 JAN – 2004 AUG)
Age*		58 (50 – 66)	58 (52 – 64)
Treatment regimen	PDS	61 (41%)	137 (100%)
	NACT	87 (59%)	0 (0%)
FIGO Stage	IIIC	124 (84%)	102 (74%)
	IV	24 (16%)	35 (26%)
Residual disease	<1 mm	97 (66%)	20 (15%)
	1-10 mm	51 (34%)	34 (25%)
	>10 mm	0 (0%)	83 (60%)
CA125 before treatment*		686 (220 – 1680)	Unknown
Overall survival*		41 (22 – not reached)	40 (26 – not reached)

* values indicate median (range of first and third quartiles).

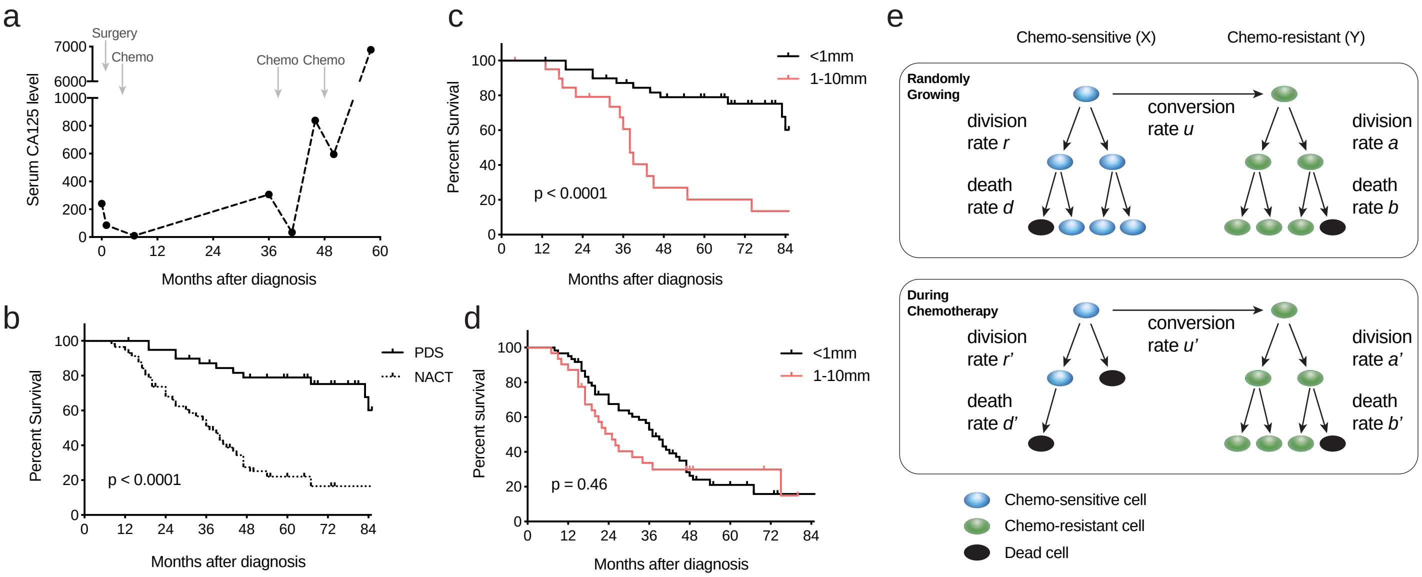

a
Surgery
Chemo
Chemo Chemo
Serum CA125 level
Months after diagnosis
b
Percent Survival
PDS
NACT
p < 0.0001
Months after diagnosis
c
Percent Survival
<1mm
1-10mm
p < 0.0001
Months after diagnosis
d
Percent survival
<1mm
1-10mm
p = 0.46
Months after diagnosis
e
Chemo-sensitive (X)
Chemo-resistant (Y)
Randomly Growing
division rate r
conversion rate u
division rate a
death rate d
death rate b
During Chemotherapy
division rate r′
conversion rate u′
division rate a′
death rate d′
death rate b′
Chemo-sensitive cell
Chemo-resistant cell
Dead cell

Figure 1

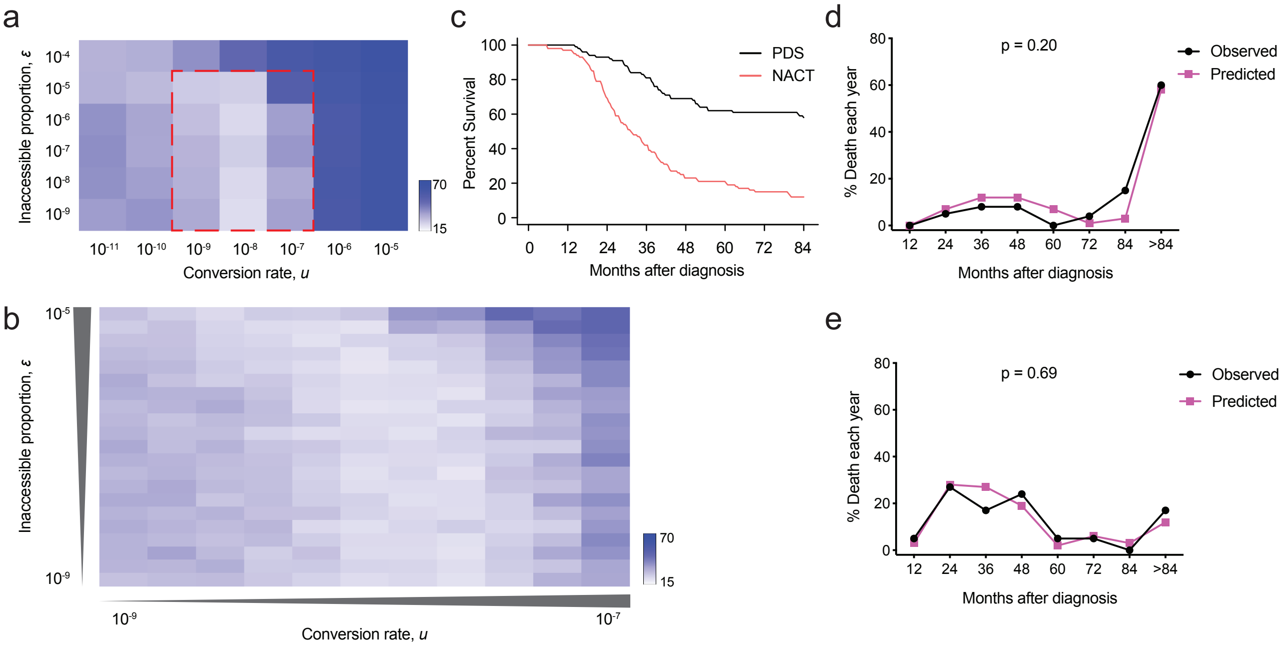

a
b
c
d
e
Inaccessible proportion, ε
Conversion rate, u
Percent Survival
Months after diagnosis
PDS
NACT
% Death each year
p = 0.20
p = 0.69
Observed
Predicted

Figure 2

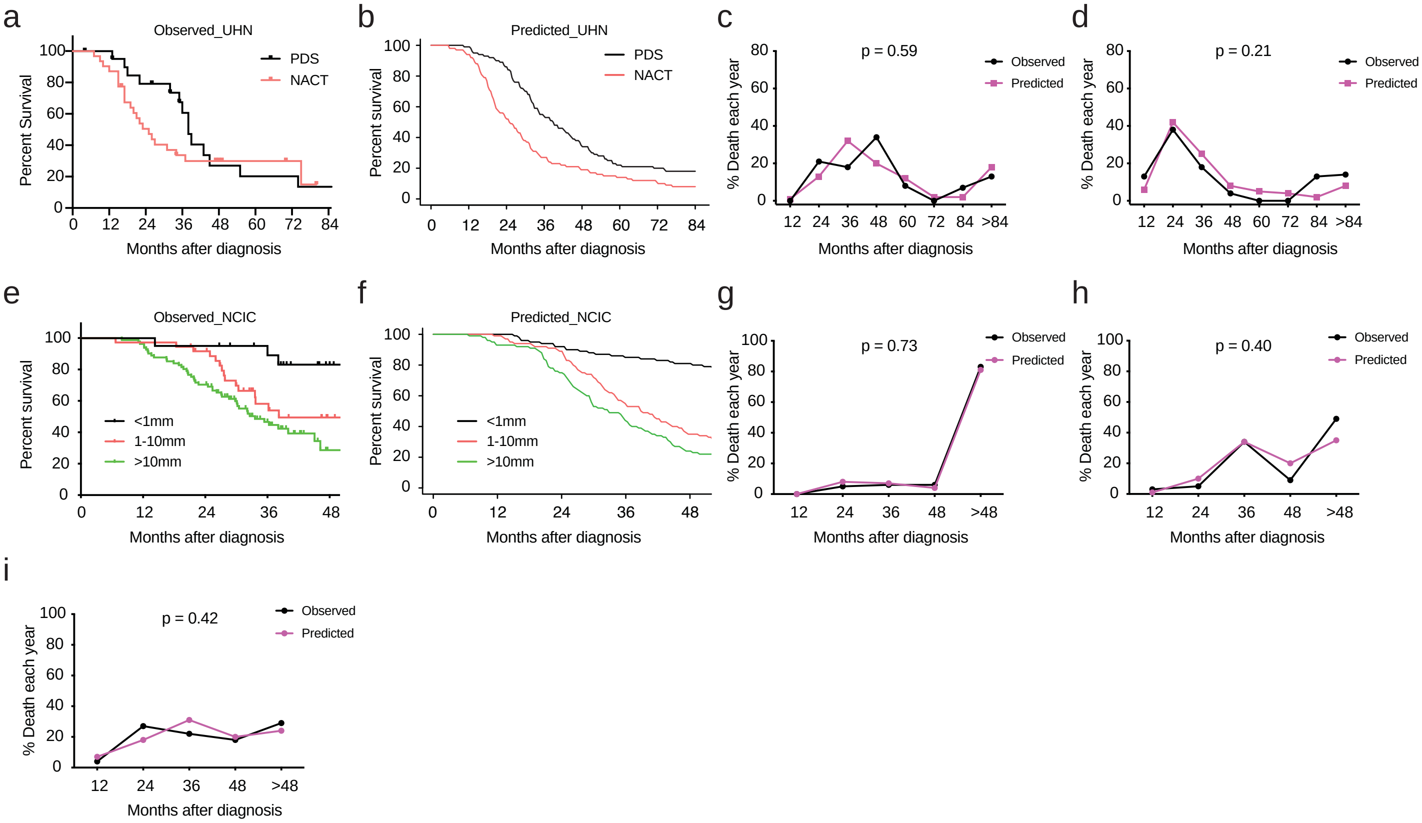

a
Observed_UHN
PDS
NACT
Percent Survival
Months after diagnosis
b
Predicted_UHN
PDS
NACT
Percent survival
Months after diagnosis
c
p = 0.59
Observed
Predicted
% Death each year
Months after diagnosis
d
p = 0.21
Observed
Predicted
% Death each year
Months after diagnosis
e
Observed_NCIC
<1mm
1-10mm
>10mm
Percent survival
Months after diagnosis
f
Predicted_NCIC
<1mm
1-10mm
>10mm
Percent survival
Months after diagnosis
g
p = 0.73
Observed
Predicted
% Death each year
Months after diagnosis
h
p = 0.40
Observed
Predicted
% Death each year
Months after diagnosis
i
p = 0.42
Observed
Predicted
% Death each year
Months after diagnosis

Figure 3

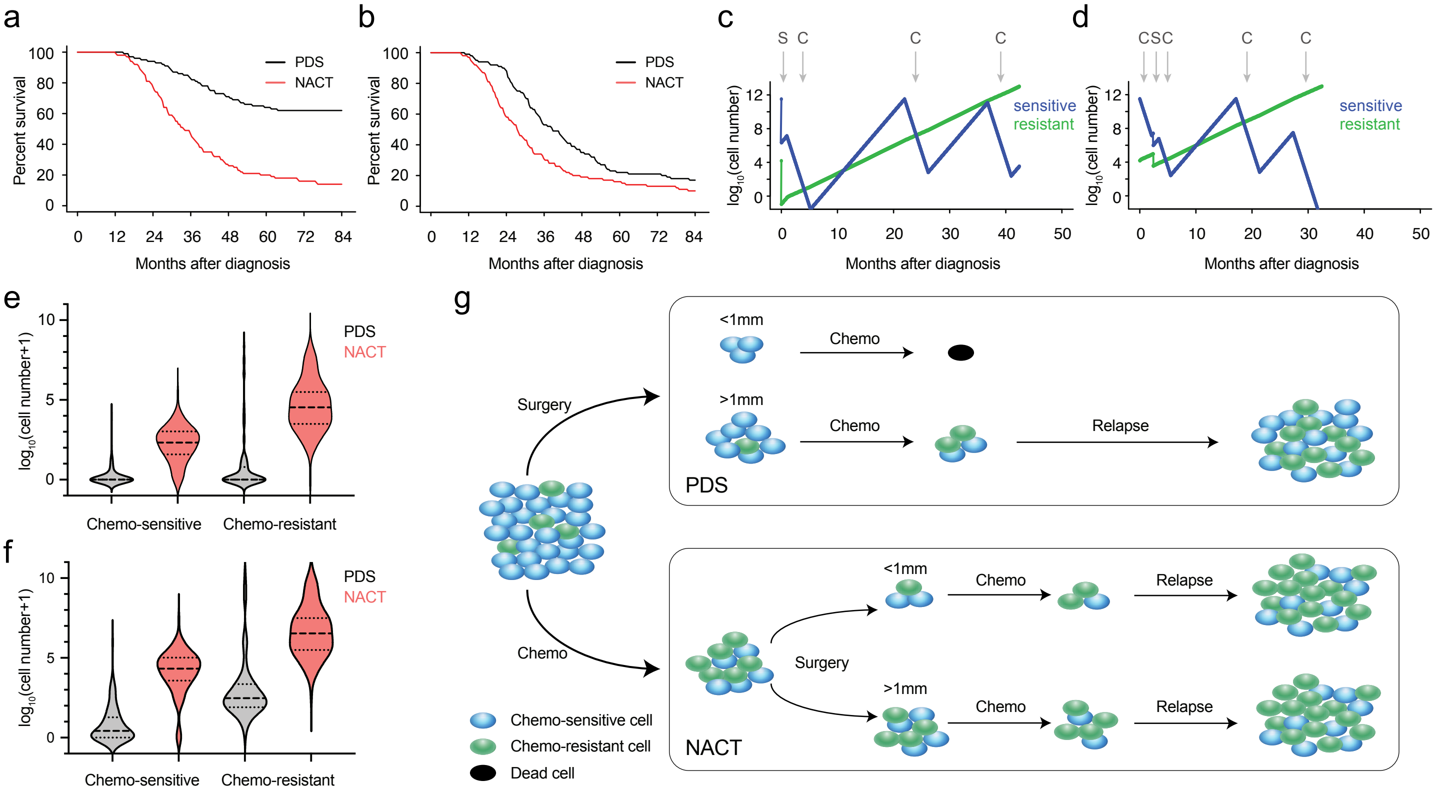
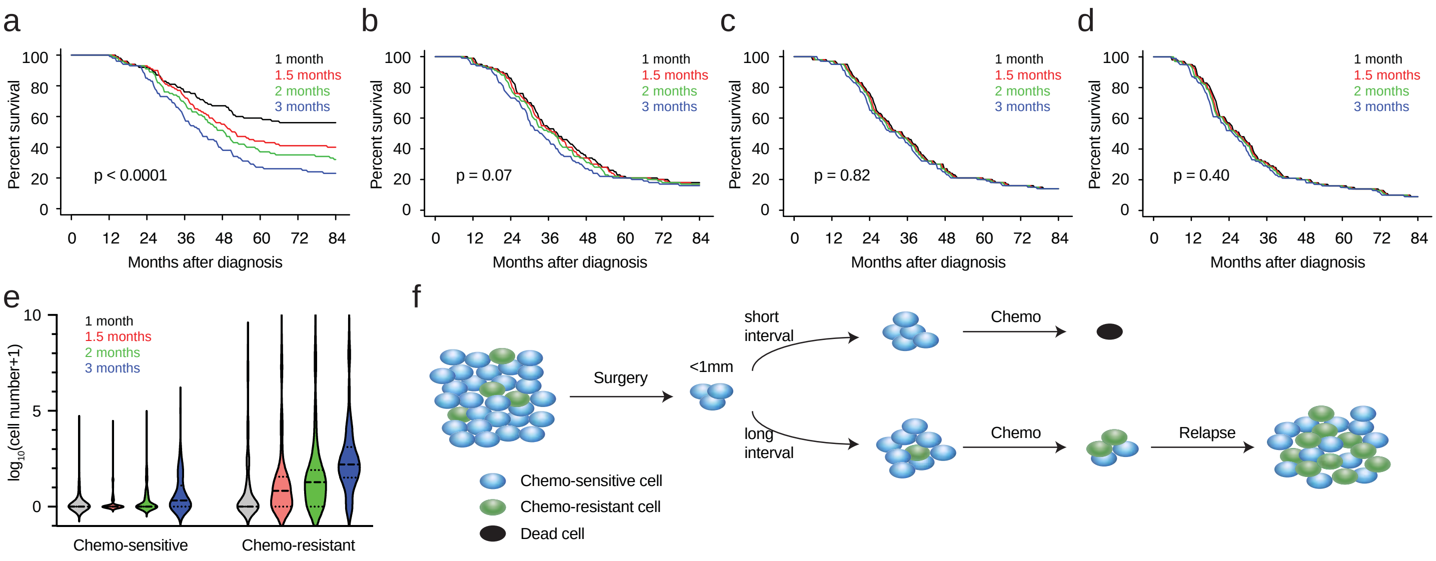
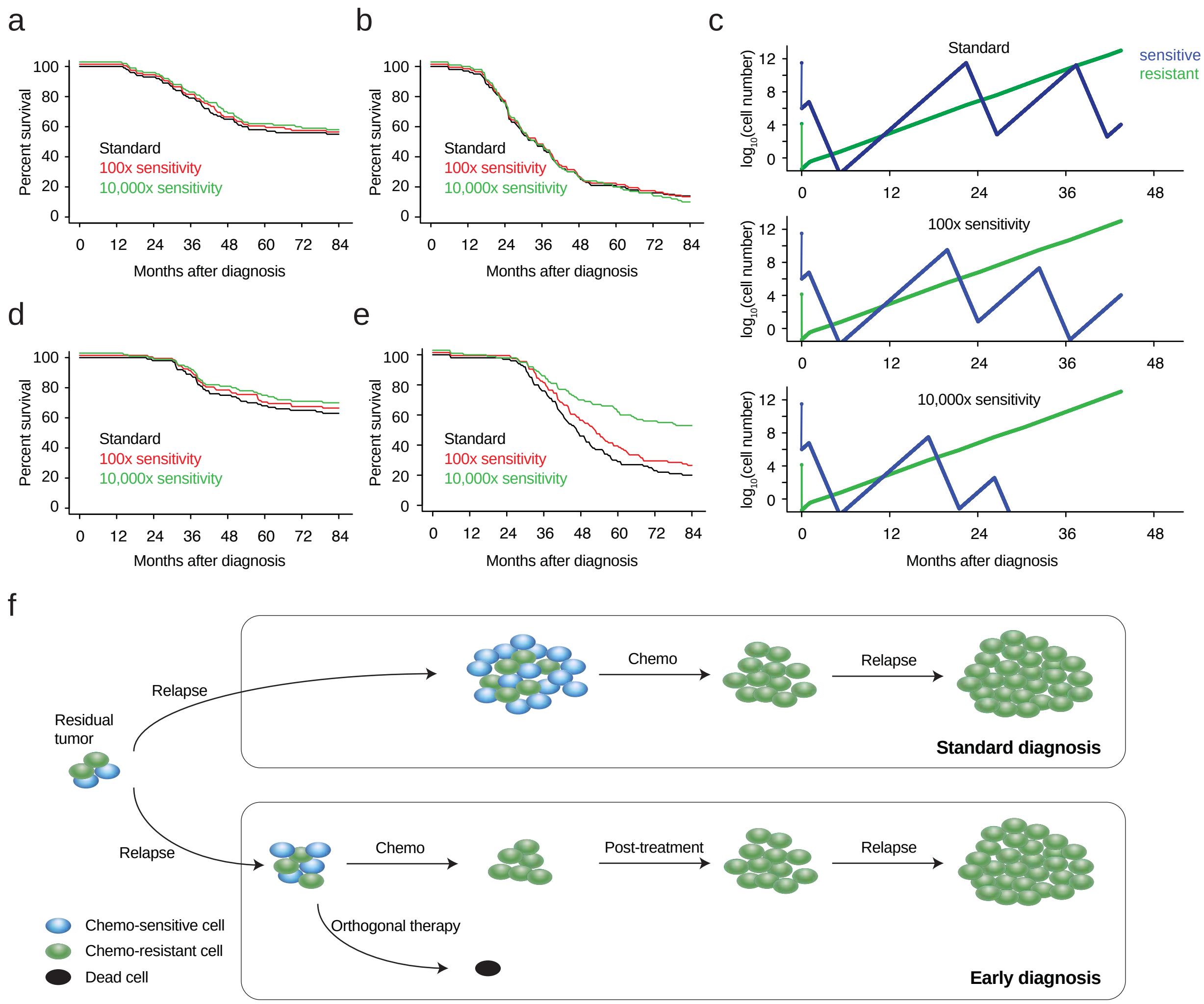

a
Percent survival
Months after diagnosis
PDS
NACT
b
Percent survival
Months after diagnosis
PDS
NACT
c
S C C C
log10(cell number)
Months after diagnosis
sensitive
resistant
d
CSC C C
log10(cell number)
Months after diagnosis
sensitive
resistant
e
log10(cell number+1)
PDS
NACT
Chemo-sensitive
Chemo-resistant
f
log10(cell number+1)
PDS
NACT
Chemo-sensitive
Chemo-resistant
g
Surgery
Chemo
<1mm
Chemo
>1mm
Chemo
Relapse
PDS
<1mm
Chemo
Relapse
Surgery
>1mm
Chemo
Relapse
NACT
Chemo-sensitive cell
Chemo-resistant cell
Dead cell

Figure 4



a
b
c
d
Percent survival
100
80
60
40
20
0
0 12 24 36 48 60 72 84
Months after diagnosis
1 month
1.5 months
2 months
3 months
p < 0.0001
p = 0.07
p = 0.82
p = 0.40
e
log10(cell number+1)
10
5
0
Chemo-sensitive
Chemo-resistant
f
Surgery
<1mm
short interval
long interval
Chemo
Relapse
Chemo-sensitive cell
Chemo-resistant cell
Dead cell

Figure 5



a
b
c
d
e
f
Percent survival
Months after diagnosis
Standard
100x sensitivity
10,000x sensitivity
sensitive
resistant
log10(cell number)
Residual tumor
Relapse
Chemo
Post-treatment
Orthogonal therapy
Standard diagnosis
Early diagnosis
Chemo-sensitive cell
Chemo-resistant cell
Dead cell

Figure 6