Prevention of Colon Cancer Recurrence From Minimal Residual Disease: Computer Optimized Dose Schedules of Intermittent Apoptotic Adjuvant Therapy

Chase Cockrell, PhD¹; Joseph Teague, BA¹; and David E. Axelrod, PhD²

PURPOSE Adjuvant chemotherapy is used after surgery for stages II and III colorectal cancer to reduce recurrence. Nevertheless, recurrence may occur years later with the emergence of initially undetected minimal residual disease (MRD). Attempts to reduce recurrence by increasing the dose intensity and increasing the time of adjuvant therapy have been limited by the adverse effects of the recommended cytotoxic agents. The goals of this study were to suggest an alternative to the recommended cytotoxic agents and to determine optimal adjuvant therapy dose schedules that would reduce the percentage of recurrence at 5 years while retaining colon crypt function.

METHODS A total of 84,400 dose schedules with different duration, interval between doses, and intensity of treatment were simulated with a high-performance computer. Simulated treatments used the drug sulindac, which had previously been used in primary prevention. With appropriate dose schedules, it can induce apoptosis at the crypt lumen surface while retaining crypt function. We used a computer model of cell dynamics in colon crypts that had been calibrated with measurements of human biopsy specimens. Proliferating mutant cells were assumed to emerge from MRD within crypts. Simulated outcomes included the recurrence percentage at 5 years and the retention of crypt function.

RESULTS Optimal dose schedules were determined for adjuvant treatment of MRD that reduced the percentage of recurrence at 5 years of stages I, II, and III colon cancer to zero.

CONCLUSION A new adjuvant therapy for colon cancer based upon optimum dose schedules of intermittent apoptotic treatment may prevent the recurrence of colon cancer from MRD and avoid the adverse effects of cytotoxic treatments.

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INTRODUCTION

The goal of our study was to reduce the probability of colon cancer recurrence after surgical resection. More than 100,000 new colon cancer cases and more than 50,000 cancer deaths were estimated to occur in the United States in 2019.¹ Treatment and adjuvant therapy for colon cancer depends upon stage. Stage I is treated only with surgical resection with the intent to cure. For stages II and III, the first treatment is surgical resection with intent to cure, followed by adjuvant chemotherapy.^{2,3} The currently recommended adjuvant combination chemotherapy includes fluorouracil, which is cytotoxic for rapidly dividing mutant cells. However, recurrence may occur for patients with any stage of colon cancer, even with adjuvant therapy.

Recurrence With Adjuvant Therapy

Several studies have compared the recurrence-free survival of patients treated with adjuvant therapy or not treated and found little or no statistically significant

difference.⁴⁻⁸ A review of 37 trials and 11 meta-analyses of adjuvant therapy with fluorouracil and levamisole or folinic acid for patients with stage II colon cancer concluded that the benefits of disease-free survival were small and that there were perhaps no benefits at all for overall survival.⁹ A review of 18 trials with more than 20,000 patients with stage II or III colon cancer who received adjuvant therapy with fluorouracil found a disease-free benefit within 2 years and long-term overall benefit that was significant but small at less than 5%.¹⁰ A review of 2,596 studies found the 5-year recurrence-free survival for patients with stage II disease was 82.7% without adjuvant therapy and 79.3% with adjuvant therapy; for stage III disease, the percentages were 49% and 63.6%, respectively.¹¹

A recent analysis of 14,325 patients in the Colorectal Cancer Registry, which includes the entire Swedish population with colorectal cancer, reported that the 5-year recurrence rate was 5.1% for patients with stage I disease who were not treated and 12.4% for those who

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CONTEXT

Key Objective

The goal of this study was to use computer simulation as proof of concept to demonstrate that adjuvant therapy could reduce the recurrence of colon cancer from minimal residual disease.

Knowledge Generated

Computer simulation results determined dose schedules that reduced 5-year recurrence to zero. Potential applications and limitations to clinical translation are discussed.

Relevance

Only a small proportion of the many simulated dose schedules was successful in reducing recurrence. This suggests the possibility that there might be alternative dose schedules and alternative drugs that would be more successful in reducing recurrence than the current dose schedules and current drugs.

were treated, 11.5% for patients with stage II disease who were not treated and 17.3% for those who were treated, and 35.5% for patients with stage III disease who were not treated and 31.7% for those who were treated. For all patients (those not treated combined with those treated), the 5-year recurrence rates were 5% for stage I, 12% for stage II, and 33% for stage III disease.¹²

Proposed New Adjuvant Therapy

Recurrence-free survival with minimum toxicity might be improved with different adjuvant therapy. We suggest an improved adjuvant therapy with 2 new aspects. The first is use of the apoptotic-inducing drug sulindac to make crypts more efficient at removing mutant cells that emerge from minimal residual disease (MRD). The second is the determination of optimal dose schedules that allow the use of maximum drug intensity while retaining colon crypt function.

METHODS

Computer Model

An agent-based computer model of stochastic cell dynamics in human colon crypts was previously described in detail.¹³ The model was calibrated with measurements of stem cells, proliferating cells, and differentiated cells in histologic sections of biopsies of the human sigmoid colon. The model behavior was validated by its ability to simulate experimentally observed crypt cell dynamics, monoclonal conversion by neutral drift, the formation of adenomas by mutant cells that may arise either at the bottom or near the top of the crypt,¹³ and the ability of crypts to recover from perturbation after exposure to cytotoxic^{14,15} or apoptotic drugs.¹⁶

The model was developed in the multiplatform open-source application NetLogo (<http://ccl.northwestern.edu/netlogo>). The NetLogo code was rewritten in C++ (available at <https://doi.org/doi:10.7282/T33X8B0H>) and ported to a high-performance computer using established methods.^{17,18} The NetLogo code is available at <https://doi.org/doi:10.7282/T3KH0QKV>.

Determination of Rates of Emergence

Parameter sweeps were used to determine the probabilities that mutant cancer cells would emerge from MRD and proliferate to produce the previously reported 5-year recurrence rates of 5% for stage I, 12% for stage II, and 33% for stage III disease.¹² Probabilities of emergence per computer step of 1×10^{-6} to 1×10^{-9} in 34 intervals were each simulated in 50 stochastic replicates for a total of 1,700 simulations. The proportion of the 50 replicates that formed an adenoma by filling the crypt with a total of 3,400 cells (adenoma) within 5 years was considered the recurrence percentage at 5 years. Probabilities of emergence of 4.5×10^{-8} , 1.61×10^{-7} , and 5.64×10^{-7} per computer step reproduced the 5-year recurrence rates of 5%, 12%, and 33%. These probabilities of emergence per computer step are listed in Table 1 as probabilities of emergence per day.

Simulation of Adjuvant Therapy

Several intermittent dose schedules of adjuvant therapy were simulated, each with a specific value of duration, interval, and treatment. Duration of adjuvant therapy treatment was varied from 1 to 24 time steps in increments of 1 step, the interval of treatment was varied from 2 to 28 steps in increments of 2 steps, and the treatment was varied from 0 to 10 steps in increments of 0.2 steps. There were 28,800 parameter sets for each of the 3 colon cancer stages, for a total of 86,400 parameter sets. Dose schedules were retained that were considered successful (ie, those that removed all mutant cells and retained crypt function [crypts did not collapse and did not increase to fill the crypt and form an adenoma]) in all 100 runs for 50 years of adjuvant therapy after surgery. An optimal dose schedule was considered one that was successful and added up to the lowest accumulated dose.

Within this context, the terms duration, interval, and treatment are defined as follows: duration of the treatment dose is the time during which cells in a crypt are exposed to the agent. The interval between doses is the time from the

TABLE 1. Probability of Emergence From MRD That Simulates the Clinically Observed Percentage of Recurrence at 5 Years
5-Year Recurrence (%)

Stage	Clinical (for no therapy and adjuvant therapy combined)		Simulated		Probability of Emergence per Day From MRD
	Mean	95% CI	Mean	95% CI	
I	5	2.9 to 7.1	4.8	3.7 to 5.9	2.39×10^{-7}
II	12	10.3 to 14.3	11.5	10.1 to 12.9	8.74×10^{-7}
III	33	29.3 to 33.1	32.8	31.0 to 34.6	3.01×10^{-6}

NOTE. Mean recurrence percentage at 5 years and 95% CIs for clinical data were recalculated from all risk factor categories for each stage in Osterman and Glimelius.¹²

Abbreviation: MRD, minimal residual disease.

beginning of 1 dose to the beginning of the next dose. Treatment is a computer model parameter (CrptDieMax) that increases the probability that a cell (normal or mutant) at the top of the crypt will die, thus reducing the size of the crypt. Proportion is the probability that a mutant cancer cell will emerge in the crypt at each computer step. Each computer step is equal to 4.5 hours. Mutant cells had a 1.16× greater probability of dividing than normal cells at the same position in the crypt and a 1.1× greater probability of dying than normal cells at the same position in the crypt.¹³

RESULTS

Recurrence Depends Upon Probabilities of Emergence From MRD

MRD is defined as 1 or more abnormal cells that remain after surgery with intent to cure. MRD may consist of 1 or more cells that are dormant and do not divide, or a small population of cells that divide and die with approximately equal rates. A proliferating population of cells may emerge from either kind of minimal disease and produce a relapsed tumor. Dormant cells may become activated and continue to proliferate, or the number of dividing cells may stochastically increase over the number of dying cells. The probability of emergence influences the rate of recurrence.

The probability of emergence from MRD can be determined as the value that simulates the clinically observed recurrence percentage at 5 years for patients with stage I, II, or III colon cancer.¹² Table 1 lists the probability of emergence that was determined to simulate the clinically observed recurrence percentage for each stage. Figure 1 shows the recurrence percentages as a function of time, and the simulated 5-year recurrence percentages are indicated.

Recurrence Depends Upon the Dose Schedule of Intermittent Apoptotic Adjuvant Therapy

To reduce the recurrence of colon cancer, we propose a novel adjuvant therapy with 2 aspects. The first is the induction of apoptosis at the top of the colon crypt, and the second is the choice of successful dose schedules. The

smaller crypts are more efficient in moving cells (both normal and mutant cells) up and out of the top of the crypt.¹⁶ The result is the removal of mutant cells that emerge from MRD before they form a tumor, which thus prevents colon cancer recurrence. Dose schedules with intense treatment that reduce the size of the crypt but do not cause the crypt to collapse need to be determined.

Intermittent dose schedules allow crypts to recover from intense treatment. Intermittent dose schedules include 3 values, duration of treatment, the interval between treatments, and the intensity of treatment. Successful intermittent treatments are those that can remove any mutant cells that have emerged from MRD and also allow crypts to recover and remain functional. For each stage (I, II, and III), 28,800 dose schedules were simulated using the corresponding probabilities of emergence listed in Table 1. A total of 86,400 dose schedules were simulated. The subset of dose schedules that were successful in removing any emergent mutant cells and that retained

FIG 1. Simulated recurrence as a function of time. The simulated 5-year recurrence percentage for stages I, II, and III are 4.8, 11.5, and 32.8 years, respectively. These reproduce the clinically observed recurrences at 5 years.¹² Numerical values for the clinically observed recurrences, the simulated recurrences, and the corresponding probabilities of emergence for each stage are given in Table 1.

FIG 2. Simulated dose schedules for (A) stage I, (B) stage II, and (C) stage III that were successful in removing all mutants while retaining stable crypt function for 50 years. For each stage, a total of 28,800 different dose schedules were simulated. The number of successful dose schedules for stages I, II, and III were 189, 97, and 46, respectively. Each dot represents 1 successful dose schedule with a specific duration of dose, interval between doses, and intensity of treatment. The color of each dot indicates the accumulated dose in 50 years. Numerical data are provided in the Excel file available at <https://doi.org/doi:10.7282/t3-bdd6-df16>.

crypt function is shown in Figure 2. Each successful dose schedule has a specific value for duration, interval, and treatment. The numerical values are provided in the Excel file available at <https://doi.org/doi:10.7282/t3-bdd6-df16>.

Recurrence Can Be Prevented by Optimal Dose Schedules of Adjuvant Therapy

Some successful dose schedules are better than others. The optimal dose schedules are those that remove any mutant cells that have emerged, retain crypt function, and have the least accumulated dose over time. The optimal dose schedules for each stage were determined by ranking the successful dose schedules by the sum of doses that accumulate over 50 years. These are listed in the Excel file available at <https://doi.org/doi:10.7282/t3-bdd6-df16>.

The dose schedule for each stage (I, II, or III) that had the least accumulated dose at 50 years was considered optimal. As an example, Figure 3 shows the percentage of recurrence of stage II over 50 years for no therapy, suboptimal intermittent therapy, and optimal intermittent therapy. Table 2 lists the duration, interval, and treatment of the optimal dose schedules for stages I, II, and III. For each stage, the optimal dose schedule reduces the percentage of recurrence at 5 years to zero. This is compared with the observed clinical adjuvant therapy 5-year recurrences of 12.4%, 17.3%, and 31.7% for stages I, II, and III, respectively.¹²

A summary of the percentage of recurrence at 5 years of the simulated optimal adjuvant therapy compared with clinically observed adjuvant therapy and no adjuvant therapy¹² is shown in Figure 4. Considering the 95% CIs, there is minimal added value with current adjuvant therapies over no therapy. This is similar to other clinical reports reviewed in the Introduction. In contrast, the simulations suggest that an optimal intermittent apoptotic adjuvant therapy may prevent recurrence of colon cancer stages I, II, and III.

DISCUSSION

The goal of this study was to use simulation as a proof of concept to demonstrate adjuvant therapy that would be most effective in reducing the colon cancer recurrence from MRD. The rate at which cells emerged from MRD was inferred from the clinically reported 5-year percentage of recurrence for each stage (I, II, and III).¹² Several intermittent dose schedules of a drug that induces apoptosis at the top of the crypt were simulated with a high-performance computer, and a subset of dose schedules for each stage was determined that could successfully

FIG 3. Comparison of recurrences of different adjuvant therapies for stage II colon cancer. No therapy is the same as that shown in Figure 1. Suboptimal intermittent therapy was simulated with dose schedules of duration of 3, interval of 24, and treatment of 1.4. Suboptimal intermittent therapy reduces recurrence, but 4% of crypts collapse. Optimal intermittent therapy was simulated with dose schedules of duration of 1, interval of 36, and treatment of 2.0. Optimal intermittent therapy of stage II prevents recurrence for 50 years with no crypt collapse. Optimal intermittent therapies for stages I and III, with appropriate dose schedules listed in Table 2, also prevent recurrence for 50 years.

TABLE 2. Percentage of Recurrence at 5 Years for Clinical and Simulated Adjuvant Therapy

Stage	5-Year Recurrence for Clinical Adjuvant Therapy (%)		Simulated Adjuvant Therapy			
	Mean	95% CI	Optimal Dose Schedules			5-Year Recurrence (%)
			Duration	Interval	Treatment	
I	12.4	2.9 to 39.0	1	32	0.5	0
II	17.3	12.0 to 17.9	1	36	2.0	0
III	31.7	30.0 to 31.9	1	42	4.5	0

NOTE. For clinical adjuvant therapy, mean recurrence percentage at 5 years and 95% CIs were recalculated from all risk factor categories for each stage listed in Osterman and Glimelius.¹² For simulated adjuvant therapy, recurrence percentage at 5 years was determined by simulation using the rates of emergence from minimal residual disease given in Table 1 and the optimal dose schedules indicated in this table. Duration of treatment and interval between treatments values are computer steps, each equivalent to 4.5 hours. Treatment is a factor that increases apoptosis at the top of the crypt.

remove all mutant cells while retaining crypt function. From among the successful dose schedules, we determined an optimal set of dose schedules that reduced the 5-year percentage of recurrence for each stage to zero.

A population of mutant cells may exist for a long time as MRD before emerging as a relapsed tumor. There are several different classes of MRD cells and different reasons why they would remain after surgery. First, MRD may consist of a small number of tumor cells that were not removed by surgery because they were not recognized as abnormal. They were histologically similar to normal tissue but molecularly different.¹⁹ Second, MRD may consist of a few dormant cells, stem-like quiescent tumor cells that become activated and emerge as a population of proliferating cells.²⁰ Third, MRD may consist of a dynamic population of cells that have an approximately equal probability of dividing and of dying, yielding a quasi-stationary

number of cells that may rarely stochastically expand in number to emerge as a relapsed tumor.²¹

We have proposed adjuvant therapy based on targeting crypts that may harbor emergent tumor cells rather than directly targeting the tumor cells. The following is our rationale for this proposed therapy. The types of cells and homeostatic cell dynamics in normal colon crypts has been well characterized.^{22,23} Quiescent stem cells reside in a niche at the bottom of the crypt, proliferating cells above them in the bottom one third of the crypt, and differentiated cells in the top two thirds of the crypt. Quiescent stem cells may become active and divide, and their progeny will move up to become proliferating cells. The proliferating cells move up to become differentiated cells. At the top of the crypt the differentiated cells undergo apoptosis and are removed. The total number of cells in a crypt is maintained at a quasi-stationary number; as cells are removed at the top of the crypt, quiescent stem cells respond by becoming active, dividing, and producing more cells to replace cells that are lost. Homeostasis is achieved, and a quasi-stationary number of crypt cells is maintained. However, if cells are removed at the top of the crypt by a drug that increases cell death at the top of the crypt, then the crypt may maintain homeostasis but with a smaller number of cells.

Such smaller crypts are more efficient in moving both normal and mutant cells up and out of the crypt. This is because any cell has a shorter path to the top of the crypt where it would be removed. An agent that increases the probability of apoptosis at the top of the crypt can make the crypt smaller. However, the effect of the apoptotic agent must be titrated so that the crypt is smaller but still has a balance between normal cell proliferation and normal cell removal; otherwise, the crypt would collapse.

The drug sulindac can make crypts smaller and more effective at removing mutant cells. It induces apoptosis at the top of colon crypts²⁴⁻²⁶ and has been shown to be effective in primary prevention of colon cancer in animal models^{25,27-29} and in combination with other agents in patients with familial adenomatous polyposis.³⁰⁻³² Additional

FIG 4. Mean recurrence percentage at 5 years and 95% CIs (horizontal bars) for stages I, II, and III. Clinical values for no adjuvant therapy and for adjuvant therapy were recalculated from all risk factor categories for each stage reported in Table 2.¹² Values for simulated therapy are listed in Table 2.

information about the effectiveness of sulindac will become available upon the completion of the Adenoma and Second Primary Prevention Trial (PACES; ClinicalTrials.gov identifier: [NCT01349881](#)). We suggest that sulindac may be effective in the prevention of colon cancer recurrence. It has been approved by the US Food and Drug Administration and is available in brand name or generic formulations. At low doses, it is used for relief of symptoms of arthritis. At high doses, and in some individuals with pre-existing conditions, it has cardiovascular and gastrointestinal risks.

With an intense constant treatment, an apoptotic drug drastically reduces the size of a crypt and causes it to collapse. However, we have previously shown that crypts can tolerate intense treatment of an apoptotic drug if the treatment is applied intermittently.¹⁶ During treatment, the crypts are reduced in size, and during the interval between treatments, the crypts recover and increase in size. The crypts oscillate in size around a quasi-stationary average number of cells, and crypt function is maintained.

A common metric of tumor relapse after surgery with the intent to cure is the 5-year percentage of recurrence. In the simulation results reported here, colon cancer recurrence at 5 years and even at 50 years after surgery was reduced to zero. We note that there are several limitations to this study. The MRD is assumed to occur within a crypt, and the cells obey the regulation of cell dynamics within a crypt. We did not know and could not account for the proportion of recurrence that occurs outside the crypt from disseminated cells and metastases. In addition, overall survival has not

been simulated, only disease-free survival as recurrence from MRD. Nevertheless, the results of 86,400 simulated dose schedules indicated that 332 dose schedules (189, 97, and 46 for stages I, II, and III, respectively) significantly reduced recurrence.

We propose a new procedure for adjuvant therapy of colon cancer based on 2 principles: (1) maintenance therapy using a drug that makes crypts smaller and more efficient in removing mutant cells once they emerge from MRD, and (2) the use of optimal intermittent dose schedules of duration of treatment, interval between treatments, and intensity of treatment. In some dose schedules simulated with a high-performance computer, the 5-year recurrence of colon cancer after surgery was reduced to zero.

We are not claiming that the simulated dose schedules that eliminated all mutants from MRD should be translated directly to patients in the clinic. However, an overview of the results of this simulation study does have direct clinical implications. Only 0.4% of the total simulated dose schedules were successful. Most simulated dose schedules (99.6%) were not successful in preventing recurrence, and the current clinical therapies are not successful in preventing recurrence. Thus, the realization that only a small proportion of the many simulated dose schedules was successful in reducing recurrence suggests the possibility that there might be alternative dose schedules and alternative drugs that would be more successful in reducing recurrence than the current dose schedules and current drugs.

AFFILIATIONS

¹Department of Surgery, University of Vermont College of Medicine, Burlington, VT

²Department of Genetics and Rutgers Cancer Institute of New Jersey, Rutgers University, Piscataway, NJ

CORRESPONDING AUTHOR

David E. Axelrod, PhD, Department of Genetics and Rutgers Cancer Institute of New Jersey, Rutgers University, 604 Allison Rd, Piscataway, NJ 08854-8082; e-mail: axelrod@biology.rutgers.edu.

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AUTHOR CONTRIBUTIONS

Conception and design: Chase Cockrell, David E. Axelrod

Financial support: Chase Cockrell, David E. Axelrod

Collection and assembly of data: Chase Cockrell, Joseph Teague

Data analysis and interpretation: Chase Cockrell, David E. Axelrod

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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