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Quantifying and Reducing Uncertainties in Cancer Therapy

Harrison H. Barrett^{a,b,c}, David S. Alberts^c, James M. Woolfenden^b, Zhonglin Liu^b, Luca Caucci^b, and John W. Hoppin^d

^aCollege of Optical Sciences, University of Arizona, Tucson AZ 85721

^bCenter for Gamma-Ray Imaging, Department of Medical Imaging, University of Arizona, Tucson AZ 85724

^cUniversity of Arizona Cancer Center, Tucson AZ 85724

^dinviCRO, Boston MA 02210

Abstract

There are two basic sources of uncertainty in cancer chemotherapy: how much of the therapeutic agent reaches the cancer cells, and how effective it is in reducing or controlling the tumor when it gets there. There is also a concern about adverse effects of the therapy drug. Similarly in external-beam radiation therapy or radionuclide therapy, there are two sources of uncertainty: delivery and efficacy of the radiation absorbed dose, and again there is a concern about radiation damage to normal tissues. The therapy operating characteristic (TOC) curve, developed in the context of radiation therapy, is a plot of the probability of tumor control vs. the probability of normal-tissue complications as the overall radiation dose level is varied, e.g. by varying the beam current in external-beam radiotherapy or the total injected activity in radionuclide therapy. The TOC can be applied to chemotherapy with the administered drug dosage as the variable. The area under a TOC curve (AUTOC) can be used as a figure of merit for therapeutic efficacy, analogous to the area under an ROC curve (AUROC), which is a figure of merit for diagnostic efficacy. In radiation therapy AUTOC can be computed for a single patient by using image data along with radiobiological models for tumor response and adverse side effects. In this paper we discuss the potential of using mathematical models of drug delivery and tumor response with imaging data to estimate AUTOC for chemotherapy, again for a single patient. This approach provides a basis for truly personalized therapy and for rigorously assessing and optimizing the therapy regimen for the particular patient. A key role is played by Emission Computed Tomography (PET or SPECT) of radiolabeled chemotherapy drugs.

Keywords

Precision medicine; personalized medicine; Therapy Operating Characteristic; chemotherapy; radiation therapy; tumor control; normal tissue complications; PET; SPECT

1. INTRODUCTION

There is considerable current discussion about the terms *precision medicine* and *personalized medicine*, and there is often a debate about which is the more appropriate adjective. National Cancer Institute Director Harold Varmus has expressed a strong preference for precision medicine. “My father thought he practiced personalized medicine,” he said. “He knew his patients personally.” One solution may be to combine the two goals, as in the recently announced Precision Medicine Initiative, subtitled Data-driven Treatments as Unique as Your Own Body.

In a technical sense, the word *precision* relates to a quantitative measurement of some parameter, and the uncertainty in the measurement is determined by both the precision and the accuracy; accuracy is defined by the average variation between the true value of the parameter and its measurement, and precision is a measure of the random difference in repeated measurements of the same parameter. In the language of statistical decision theory, a measurement is an *estimate* of the parameter, the precision is specified by the variance of the estimate and the accuracy (bias) is specified by its mean over repeated measurement in comparison to the true value. In many settings, including imaging, the *measurement* must include not only instrumental outputs but also further processing of the outputs to get the desired estimates. Uncertainties might then be reduced by choosing the measuring instrument and the data processing in such a way as to reduce the bias and/or variance of the estimate.

In imaging, however, it is only rarely possible to find an unbiased estimate of any parameter of interest, at least if the parameter is defined in terms of the object being imaged rather than the image itself. It is one thing to say how big a tumor appears to be in an image, quite another to say how big it is in the patient’s body. Imaging systems always have *null functions*, components of the object that do not contribute to the image data; many objects can give the same image, so no unique bias can be defined.^{1,2}

One way around this conundrum is to recognize that the goal of medical imaging is to diagnose and treat the patient. Quantitative estimates are often useful, but mainly as a stepping stone to diagnosis or treatment. The ultimate standard, in this approach, is diagnostic or therapeutic efficacy,²⁻⁴ defined as averages over large groups of patients.

Personalized medicine, on the other hand, strives to get the best possible outcome for a *particular* patient, so a second conundrum arises: If efficacy is defined for a group of patients, what can it possibly mean to optimize efficacy for a particular patient, and how can you prove you have done so?

Answers to these questions in the context of cancer therapy are given in Sec. 5 of this paper, but first we survey, in Sec. 2, the broad range of uncertainties that must be addressed in any rigorous analysis of personalized cancer therapy. Then, in Sec. 3, we discuss Therapy Operating Characteristic (TOC) curves.^{5,6} In radiation therapy, a TOC curve is a plot of the probability of tumor control vs. the probability of specified normal-tissue complications as the overall radiation dose level is varied, e.g. by varying the beam current in external-beam radiotherapy or the total injected activity in radionuclide therapy. The TOC can be applied to

chemotherapy with the administered drug dosage as the variable. The area under a TOC curve, denoted AUTO C, can be used as a figure of merit for therapeutic efficacy, analogous to the area under an ROC curve (AUROC), which is a figure of merit for diagnostic efficacy.² In radiation therapy we have shown^{5,6} that AUTO C can be computed for a single patient by using image data along with radiobiological models for tumor response and adverse side effects. These radiobiological models and other mathematical models relevant to radiation therapy and chemotherapy are briefly reviewed in Sec. 4.

In Sec. 5 we introduce the concept of posterior probability, which underlies all forms of personalized therapy. The word *posterior* in this context refers to our knowledge of an individual patient *after* we have acquired the images and clinical or genomic data needed to plan the personalized therapy. Though often associated with Bayesian statistics and hence regarded as subjective, we argue in Sec. 5 that posterior probabilities and conclusions drawn from them are amenable to verification by clinical trials.

In Sec. 6 we exploit the analogies to ROC theory further and develop methods for computing the posterior probabilities and relating them to probability of tumor control. A summary and recommendations for future research are given in Sec. 7.

2. UNCERTAINTIES IN CANCER THERAPY

2.1 Chemotherapy

Cancer cells can develop resistance to chemotherapy drugs in many ways. Von Ho and colleagues⁷ distinguish biological and physiological resistance; biological resistance describes the response of the tumor cells to the drug, and physiological resistance concerns delivery of the drug to the tumor cells.

One mechanism of biological resistance, emphasized by Gottesman,⁸ is molecular efflux pumps such as P-glycoprotein (P-gp), a cell-membrane protein that is overexpressed in many cancer cells. P-gp recognizes small cationic molecules, including many chemotherapy drugs, and recruits energy from ATP to expel them. Other patient-specific genetic factors that lead to drug resistance include gene mutations, gene amplification or epigenetic changes.⁹ Both the pH and the oxygenation of the tumor also have a significant impact on drug resistance.

Factors that impede drug delivery include the complicated, tortuous nature of tumor vasculature; the biochemical signals that control the vessel permeability; and the fibrotic stroma that results from desmoplastic reaction in the extracellular space. For targeted chemotherapeutic agents we must also consider the end-game processes of receptor binding; internalization of the drug into the cell; catabolism (breakdown of the drug) and residualization back into the extracellular space.

The patient-to-patient variations in drug delivery are potentially very large. Gurney¹⁰ estimates that there is a 4-10 fold variation among individuals in cytotoxic drug clearance from serum, and there is further variation in vascular permeability, internal tumor pressure and transport of the drug to the tumor cells. This enormous range of patient-specific variation means that some patients will suffer unnecessary toxic side-effects and others will

get less than the requisite therapeutic dose to the tumor. In clinical trials, this same variability can lead to a drug being declared ineffective when it would, in fact, be very effective if administered with the proper dosage and route for each patient. Current practice in medical oncology is personalized by attempting to tailor the drug to the tumor genomics, but there is a need to quantify and optimize the amount of drug delivered.

All of the physiological or biological factors that influence tumor response can be *heterogeneous*, in the sense that they can be different for different cells or for different locations in the tumor, and all forms of heterogeneity can themselves lead to drug resistance. In brief, cells that happen to have some degree of biological resistance or which are located in a region of low perfusion can survive a chemotherapy treatment and produce resistant clones.^{11,12}

Another concern in chemotherapy is drug-induced damage to normal tissues. For example, cardiac damage is a common side effect of doxorubicin, and kidney damage can occur with renally excreted drugs.

Many molecular imaging methods can be used to study these mechanisms in basic biomedical research or clinical trials, but if we want to do personalized chemotherapy on a routine basis, we can perform only a few imaging studies on an individual patient. Ideally, we would do just one imaging study, and we would extract as much information as possible from it. It is a premise of this paper that imaging the transport of a radiolabeled chemotherapy agent at high spatial and temporal resolution can significantly reduce the uncertainties associated with chemotherapy when used with appropriate mathematical models.

2.2 Radiation therapy with external beams

Tumors can be treated with beams of photons, electrons, protons, neutrons or heavy ions. Clinical practice with these therapies is to use images of the patient to identify the regions occupied by the tumor and by normal organs, then to plan a therapy that will deliver a cytotoxic radiation dose to the tumor and tolerable doses to critical normal organs. In this sense routine external-beam radiation therapy is already much more personalized than most chemotherapy.

Another key difference is that delivery of a radiation dose is much more precise than delivery of a chemotherapeutic dose. The distribution of the electron density in a patient can be derived from a CT scan, and then the spatial and temporal distribution of the absorbed dose, measured in grays, can be computed from basic physics and knowledge of the beam parameters for the particular patient. The uncertainties in delivery of a radiation dose are much less significant than the uncertainties in delivering a chemotherapeutic dose. Moreover, the uncertainties in the biological effects of the radiation dose can be assessed with some precision through the use of mathematical radiobiological models.

Collateral damage to normal tissues in external-beam radiation therapy is likely to be confined to the vicinity of the tumor being treated, so we should be able to identify the main

organs at risk. For example, in treating prostate cancer, it is important to minimize radiation dose to the rectum and colon.

Radiation therapy can also have nonlocal impact through *bystander* and *abscopal* effects, mediated largely by stimulation of the immune system. For a recent review of these topics, see Sologuren et al.¹³

3. METRICS OF THERAPEUTIC SUCCESS: TOC CURVES

3.1 TOC curves and their application in radiation therapy

As noted in the introduction, a Therapy Operating Characteristic (TOC) curve is a plot of the probability of tumor control, denoted $\Pr(TC)$, vs. the probability of normal-tissue complications, $\Pr(NTC)$, as the overall radiation dose level is varied. The mathematical and computational aspects of TOC curves are treated in detail in Barrett et al. (2013),⁶ the sixth in a series of theoretical papers on Objective Assessment of Image Quality, hence referred to as OAIQ VI. Two schematic TOC curves are depicted in Fig. 1.

OAIQ VI uses the area under the TOC curve (AUTOC) as a figure of merit for radiation therapy planning and for the imaging components that affect the plan. An AUTOC of 1.0 is ideal, and $\text{AUTOC} = 0.5$ corresponds to a treatment scenario in which the probability of tumor control can be increased only at the expense of an identical increase in the probability of normal-tissue complications. In contrast to ROC, an $\text{AUTOC} \ll 0.5$ can also occur, in the case of a very bad treatment plan where there is a large probability of damage to normal tissues with little chance of tumor control.

Much work has gone into estimating $\Pr(TC)$ and $\Pr(NTC)$,¹⁴⁻¹⁹ and standardized modules for their calculation are freely available.^{20,21}

As detailed in OAIQ VI, AUTOC can be used for:

- Evaluation of image quality in terms of therapeutic efficacy
- Comparison of treatment regimens for a population of patients
- Evaluation of segmentation algorithms⁵
- Study of the effects of patient motion during beam therapy
- Study of the usefulness of auxiliary data, such as hypoxia images
- Evaluation of stem cells and viruses as vectors for radionuclide therapy
- Optimization of the treatment plan for an individual patient

To use AUTOC as a figure of merit for personalized radiation therapy, we need:

- Image data from an individual patient
- Treatment plan tailored to the patient
- Calculated distribution of radiation absorbed dose (in Gy)
- Credible radiobiological models for $\Pr(TC)$ and $\Pr(NTC)$

3.2 Extension of TOC methodology to chemotherapy

To compute $\text{Pr}(TC)$ as function of administered chemotherapeutic dose for a specific patient, we need

- Mathematical models for drug delivery
- Mathematical models for drug response
- Image data from which to estimate free parameters in the models
- Efficient estimation methods
- Methods to estimate uncertainty of parameter estimates and resulting uncertainty in delivery and response

One way to get the needed image data for estimating $\text{Pr}(TC)$ is to use radiolabeled therapeutic agents, or validated surrogates, at subtherapeutic dose and acquire dynamic PET or SPECT images. For example, there is considerable current interest in antibody-drug conjugates, in which a monoclonal antibody can be linked to either a radionuclide or a chemotherapy drug. The ability of the antibody to target its antigen is essentially unchanged by the addition of a small molecule, provided the binding site is not obstructed by the conjugate.

The concept of radiolabeling chemotherapy agents to assess targeting is not new. Pilot studies go back to the mid-1970s, when Walter Wolf at USC proposed using Pt-195m-labeled cisplatin,²²⁻²⁴ and a group at the University of Arizona used Co-57 bleomycin (although not specifically to evaluate targeting).^{25,26} The related approach of using the same agent at low dose for diagnostic imaging and at high dose for therapy is also not new. The best exemplar is probably I-131 sodium iodide in differentiated thyroid carcinoma (or, alternatively, I-123 for diagnosis and I-131 for therapy). A variation on this theme is exemplified by I-131 tositumomab (Bexxar) in B-cell lymphoma, where the initial low dose provides quantitative image data for radiation-dose estimation, and the therapy dose is derived from these data so as to limit bone-marrow toxicity. Another variation on this theme was In-111-ibritumomab (Zevalin) for imaging and Y-90-Zevalin for therapy of B-cell lymphoma and certain other non-Hodgkin lymphomas. Zevalin has another interesting property, namely that the molecule without Y-90 and its chelating linker is essentially the same as rituximab (Rituxan), a standard chemotherapy drug for lymphoma.

The abscissa on a chemotherapy TOC curve, $\text{Pr}(NTC)$, depends on the type and amount of the therapeutic drug, and of course on the patient and the particular adverse effect considered, but it does not depend on the parameters that drive $\text{Pr}(TC)$. The only apparent way of getting a personalized $\text{Pr}(NTC)$ is to make use of databases of adverse effects in chemotherapy and stratify them according to the clinical history, tumor stage and other characteristics of the patient. This line of research is beyond the scope of this paper, and henceforth we will concentrate on getting patient-specific estimates of $\text{Pr}(TC)$.

4. MATHEMATICAL MODELS FOR DRUG DELIVERY

In this section we survey models that have been used or suggested as descriptions of the major intratumoral processes: extravasation, diffusion, binding and internalization. To set the stage, we begin with a discussion of the three-dimensional time-dependent diffusion equation.

4.1 Diffusion equation

The time-dependent diffusion equation for an infinite uniform medium is

$$\left[\frac{\partial}{\partial t} - D \nabla^2 \right] f(\mathbf{r}, t) = s(\mathbf{r}, t), \quad (4.1)$$

where $f(\mathbf{r}, t)$ is the concentration of the diffusing species (e.g., a radiotracer) at point $\mathbf{r}$ and time t , $s(\mathbf{r}, t)$ is the source of this species, and D is the diffusion coefficient. Note that $f(\mathbf{r}, t)$ has units of inverse volume or inverse length cubed, which we write as $[f] = 1/L^3$, where [...] is read “dimensions of ...”. The source $s(\mathbf{r}, t)$, on the other hand, is a rate of change of concentration, $[s] = 1/(L^3 T)$ (T = time). Thus $[D] = L^2/T$.

We can solve this equation in terms of the Green's function, $G(\mathbf{r}, \mathbf{r}'; t, t')$, which must satisfy

$$\left[\frac{\partial}{\partial t} - D \nabla^2 \right] G(\mathbf{r}, \mathbf{r}'; t, t') = \delta(\mathbf{r} - \mathbf{r}') \delta(t - t'). \quad (4.2)$$

It can be shown that

$$G(\mathbf{r}, \mathbf{r}'; t, t') = \frac{\text{step}(t - t')}{[4\pi D(t - t')]^{3/2}} \exp \left[-\frac{|\mathbf{r} - \mathbf{r}'|^2}{4D(t - t')} \right]. \quad (4.3)$$

If the source function is known, the solution to (4.1) is

$$f(\mathbf{r}, t) = \int_{\infty} d^3 r' \int_{-\infty}^t dt' G(\mathbf{r}, \mathbf{r}'; t, t') s(\mathbf{r}', t'). \quad (4.4)$$

where the subscript ∞ on the integral indicates that it runs over the infinite 3D domain.

To illustrate the results of this equation, we considered diffusion of an antibody of molecular weight 150 kDa from the point of extravasation in the tumor to an observation point 100, 200 or 400 μm away. In accord with Nugent and Jain,²⁷ we took the diffusion coefficient in the tumor to be $10^{-7} \text{ cm}^2/\text{s}$, and we considered spherical shells of capillaries surrounding the observation point, so that the source strength in the diffusion equation was proportional to $|\mathbf{r} - \mathbf{r}'|^2$. The resulting plots of antibody concentration vs. time are shown in Fig. 2. Note that the horizontal axis in this plot extends to 100 minutes; though equilibration of the drug concentration in major blood vessels might occur rapidly, equilibration within the tumor capillary bed is quite slow.

If the diffusion coefficient is a function of location within a tumor, (4.3) becomes

$$\frac{\partial}{\partial t} f(\mathbf{r}, t) - \nabla \cdot [D(\mathbf{r}) \nabla f(\mathbf{r}, t)] = s(\mathbf{r}, t). \quad (4.5)$$

For small deviations of D about a constant value, it is useful to write $D(\mathbf{r}) = D_0 + \delta D(\mathbf{r})$, and in this case the solution can be approximated by a Born series, possibly retaining only the first term.

4.2 Application to radiotracer diffusion in solid tumors

In emission imaging with radioactive materials, the object is often defined as activity per unit volume, where activity is expressed in becquerels (Bq) or nuclear disintegrations per second. If we denote the time-dependent activity per unit volume as $a(\mathbf{r}, t)$, then $a(\mathbf{r}, t) = f(\mathbf{r}, t)/\tau$, where τ is the exponential-decay time constant of the radioisotope, in seconds. The more familiar half-life is given by $T_{1/2} = \tau \ln 2$. In what follows we denote the object as $f(\mathbf{r}, t)$. If there is one radioactive nucleus per tracer molecule, then $f(\mathbf{r}, t)$ is the mean number of molecules per unit volume at point $\mathbf{r}$ and time t .

In kinetic studies with a radiotracer, $f(\mathbf{r}, t) = 0$ before the injection of the tracer, which we take to be at time $t = 0$. After this time, the concentration of the tracer in blood vessels is denoted $c(\mathbf{r}, t)$.

The rate at which the tracer escapes from the vessels and enters the interstitium depends on both the vascular permeability and the tumor vascularity. The vascular permeability is defined as the molecular flux (molecules per unit area per second) through the vessel wall divided by the concentration (molecules per unit volume) within the vessel. Thus the permeability has dimensions of L/T , and it is frequently expressed in cm/s.

The source term in the diffusion equation must account for the plasma concentration, the permeability and the total capillary area per unit volume through which the extravasation can occur. Within a given volume, this area depends on the number of capillaries and their average diameter. Thus we can write

$$s(\mathbf{r}, t) \equiv c(\mathbf{r}, t) v(\mathbf{r}), \quad (t \geq 0), \quad (4.6)$$

where the *vascular factor* $v(\mathbf{r})$ (assumed to be independent of time during an imaging session) can be interpreted as the average permeability times the average number of vessels per unit volume times the average area-to-volume ratio of the vessels, so that $[s] = 1/(L^3T)$ as required for dimensional consistency in (4.1).

With (4.6), (4.4) becomes

$$f(\mathbf{r}, t) = \int_V d^3r' \int_0^t dt' G(\mathbf{r}, \mathbf{r}'; t - t') c(\mathbf{r}', t') v(\mathbf{r}'), \quad (4.7)$$

where V is the volume occupied by the tumor.

4.3 Models for tumor vascularity and permeability

Many current treatments of drug delivery trace back to the 1919 work of Nobel Laureate August Krogh on oxygen transport. The Krogh cylinder model²⁸⁻³⁰ represents the capillaries as a regular array of uniform cylinders, and it assumes that any point in the tumor is perfused by only one such model capillary.

More realistic models of tumor capillaries are given in numerous papers by Rakesh Jain and coworkers, and in particular the fractal model given by Baish and Jain³¹ captures the complexity of the problem with a small number of free parameters.

Compartmental pharmacokinetics (CPK) is also commonly used, but it is not well suited to the purposes of this paper. A compartment is a defined volume of tissue within which there are no spatial gradients (there are no spatial derivatives in the CPK equations) and where equilibrium concentrations within the compartments are reached essentially instantaneously. Moreover, it is assumed that the plasma concentration of the drug is the same at all points in the subject. Departures from the CPK assumptions, including nonequilibrium processes and spatial gradients, can result in heterogeneity of the drug distribution and reduced efficacy of the therapy. Treating the tumor cells collectively as a single compartment is unrealistic, and doing CPK on a voxel-by-voxel basis neglects communication between voxels by routes other than the common arterial supply. The time scales in Fig. 2 show that there are long delays between a change in arterial concentration and delivery of a drug to a point in a tumor; the arterial input function, a critical part of CPK analysis, has very little to do with the time dependence of the interstitial concentration within a tumor capillary bed.

4.4 Binding and internalization in targeted therapy

Binding of a ligand to a receptor is conventionally parameterized by the receptor number B_{max} (receptors per cell), the affinity K_d and the binding potential B_{max}/K_d . In equilibrium, there is a simple relation between K_d and the fraction of targeted drug molecules or other ligands bound to their receptors, but it is difficult to know whether equilibrium conditions prevail.

Nonequilibrium reaction-diffusion models such as the Smoluchowski and Doi models are reviewed by Agbanusi et al.³²

Internalization takes place through endocytosis or transmembrane receptors; for a discussion of the mathematics of endocytosis and its relation to signalling, see Birtwistle.³³

4.5 Concentration distribution in a tracer study

When all of these processes are active in a radiotracer study, we can write the total concentration (molecules per unit volume) of the radionuclide as

$$f(\mathbf{r}, t) = f^c(\mathbf{r}, t) + f^d(\mathbf{r}, t) + f^b(\mathbf{r}, t) + f^i(\mathbf{r}, t), \quad (4.8)$$

where the four terms represent, respectively, the concentrations in the capillaries (superscript c); diffusing in the tumor interstitium (d); bound to cell-surface receptors (b), and internalized into the cytoplasm (i). In a dynamic PET or SPECT study, all of these terms

contribute to the image data but with different time dependences, so in principle they can be separated.

5. POSTERIOR PROBABILITIES

We now return to the basic problem of personalized medicine, as posed in the Introduction: Both diagnostic and therapeutic efficacy are defined for a large population of patients. What does it mean to optimize the results for one patient? How can we verify that we have done so? Specifically for personalized chemotherapy, how can we vary the administered drug dosage or regimen so as to get the best possible therapeutic outcome for an individual patient?

Similar questions arise in diagnostic imaging: How can we vary the imaging system configuration or data-acquisition protocol so as to get the best possible diagnostic information for an individual patient? A general approach to answering this question for adaptive (personalized) SPECT imaging was given by Barrett et al.,³⁴ and it was extended to more general adaptive and multimodality imaging systems by Clarkson et al.³⁵ The general schema for personalized medicine is illustrated, for both diagnostic imaging and therapy, in Fig. 3. The key is to define two theoretical infinite ensembles of patients, called the *prior ensemble* and the *posterior ensemble*.

One way to think of a prior ensemble is that it is a population on which clinical trials can be performed. For a trial of a chemotherapy drug, for example, a set of inclusion criteria is specified and some endpoint or outcome is defined. The set of all patients who satisfy the inclusion criteria is the prior ensemble, in the present language, and the actual cohort for the trial is a random sample from this ensemble. Often this cohort is divided into two groups (*arms*), in one of which the patients receive the drug under test and in the other they receive a different drug. The two drugs may have different standard dosages (mg/m^2) and administration schedules and other protocol factors, but all patients in the same arm receive identical treatment.

In personalized chemotherapy, by contrast, we perform genetic profiling, blood tests and imaging studies to obtain detailed information on each patient, and we use that information to alter the protocol. Depending on what information is acquired, the protocol alterations can include changing the dosage or administration schedule; pharmacological interventions such as P-gp suppressors or stromal modulators; methods of increasing oxygenation or pH of the tumor, or even choosing different drugs or drug combinations.

With this approach we have a different protocol for each patient. Does that rule out the possibility of clinical trials? No. We just have to rephrase the question to be answered by the trial. A conventional drug trial asks whether drug A with protocol 1 is better than drug B with protocol 2. Now we can ask whether drug A with a protocol adapted to the patient is better than drug A with a fixed protocol. In other words, does personalized therapy really work? The adaptation (personalization) strategy is an algorithm for deciding how to change the protocol from patient to patient, much as we now adapt the dosage to body surface area. We can think of the adaptation strategy as a meta-protocol, and we can perform clinical trials not with fixed protocols but with fixed meta-protocols. With two drugs, we can adapt

each to the patient and ask if drug A with a protocol adapted to the patient is better than drug B with a different protocol adaptation to the same patient.

This process can be repeated for multiple patients drawn from the same prior ensemble in order to answer the questions posed in the previous paragraph, and standard methods can be used to assess the statistical significance of the conclusions.

Similar considerations apply to adaptive diagnostic imaging, as indicated in Fig. 3, and we can summarize the paradigm in both cases as:

- Obtain patient-specific images and other data
- Optimize the final imaging system or therapy regimen for the posterior ensemble
- Evaluate the result with samples from the prior ensemble

A key point is that the second step requires mathematical models for diagnostic or therapeutic efficacy, perhaps as expressed by AUROC or AUTOC. Another important point is that the images required for chemotherapy optimization must be dynamic molecular images of the chemotherapeutic drug itself or a surrogate known to have the same kinetic behavior.

6. COMPUTATIONAL METHODS

In Sec. 3.2, we suggested collecting dynamic SPECT or PET images with a small, subtherapeutic amount of a radiolabeled chemotherapy drug in order to obtain information about drug delivery for a particular patient, denoted patient j . Let the set of all such dynamic images acquired for patient j be denoted $\mathbf{G}_j$. For actual therapy, we would use the same drug, probably without the radioactive label, and administer a much larger amount. If we assume that mass M_j of the drug will be administered to this patient for the therapy, then both the probability of tumor control and the probability of a normal-tissue complication will increase monotonically with M_j , so we can take M_j as the control variable on a TOC curve for chemotherapy.

To construct the TOC curve for patient j , we need the conditional probabilities $\Pr(TC/M_j, \mathbf{G}_j, j)$ and $\Pr(NTC/M_j, \mathbf{G}_j, j)$. The tumor-control probability $\Pr(TC/M_j, \mathbf{G}_j, j)$ is the probability of tumor control given that images $\mathbf{G}_j$ were obtained in the tracer study and that mass M_j of the drug was administered to patient j in the therapeutic step. The final j in $\Pr(TC/M_j, \mathbf{G}_j, j)$ is included so that clinical or genomic data about patient j can be used, along with the image data, in estimating the TC probability.

Current clinical practice in chemotherapy is to choose the administered dose to be proportional to the patient's body surface area, with no information about the processes that limit dose delivery to the tumor cells. As databases become ever larger and more accessible, it should be possible to construct good estimates of $\Pr(TC/M)$ and $\Pr(NTC/M)$ for the prior ensemble of all patients who have received a specific drug for a specific type, stage and grade of tumor. These estimates will depend on the definition of tumor control and the type and magnitude of the normal-tissue effects considered, and of course they vary with the

administered mass (or mass per unit patient area) of the drug, but they should provide a reasonable characterization of the prior ensemble.

Moreover, if we assume that the dynamic images cover just the tumor region, then these same clinical data immediately give us the *posterior* probability of normal-tissue complications, after the dynamic ECT images are acquired, simply because the images provide no information relevant to normal-tissue complications. Posterior and prior are identical in this case, so $\Pr(NTC/M_j, \mathbf{G}, j) = \Pr(NTC/M_j, j)$. Again, the final j in this expression indicates that $\Pr(NTC)$ can still depend on characteristics of the specific patient; for example, cardiac function tests can be used to assess the patient's propensity for cardiotoxicity after doxorubicin therapy.

6.1 Analogy to ROC analysis; linear discriminants

ROC analysis is used to measure the performance of some observer or decision maker on binary classification tasks, where a data set must be associated with one of two possible classes, say class C_1 and class C_2 (e.g., tumor absent and tumor present). In medical imaging the *observer* can be radiologist, a computer algorithm or a mathematical construct called the *ideal observer*, and the data consist of one or more images, denoted $\mathbf{g}$.

Under broad conditions,¹ it can be shown that the decision strategy of any algorithmic observer given data $\mathbf{g}$ can be construed as first computing a scalar-valued functional of the data, denoted $\tau \equiv T(\mathbf{g})$ and then making the decision by comparing it to a decision threshold τ_0 as follows:

$$\begin{array}{c} D_2 \\ > \\ \tau < \\ < \\ D_1 \end{array} \quad \tau_0. \quad (6.1)$$

This inequality is to be read, “make decision D_2 (i.e., choose class C_2) when the greater-than sign holds; make decision D_1 (choose class C_1) when the less-than sign holds.” Human observers fit into this same paradigm if we allow a random component, called *internal noise*, in the decision variable τ . The scalar τ is called the *test statistic*, and $T(\mathbf{g})$ is the *discriminant function*.

The probability of the observer making decision D_2 when the data set was produced from an object in class C_2 , known as the true positive fraction or TPF, is given by¹

$$TPF \equiv \Pr(D_2|C_2) = \Pr(\tau > \tau_0|C_2) = \int_{\tau_0}^{\infty} d\tau \quad \text{pr}(\tau|C_2) = \int_{\tau_0}^{\infty} d\tau \int d\mathbf{g} \quad \text{pr}(\tau|\mathbf{g}) \quad \text{pr}(\mathbf{g}|C_2), \quad (6.2)$$

where $\text{pr}(\cdot)$ denotes *probability density function* (PDF) and $\text{pr}(\cdot|\cdot)$ is a conditional PDF.

TOC analysis for chemotherapy has this same structure. The tumor itself can be regarded as the observer, and the data set to which it responds is the drug distribution in the tumor, which we denote as $F(\mathbf{r}, t)$. If the administered dose in both the radiotracer step and the therapy were small enough to avoid saturating the receptors, $F(\mathbf{r}, t)$ would be just the ratio of the

injected masses times the tracer concentration $f(\mathbf{r}, t)$ discussed in Sec. 4, but a nonlinear relation is expected in general.

As in (4.8), the drug distribution consists of molecules in the capillaries, freely diffusing molecules and ones either bound to receptors or internalized into the cytoplasm, so we can write

$$F(\mathbf{r}, t) = F^c(\mathbf{r}, t) + F^d(\mathbf{r}, t) + F^b(\mathbf{r}, t) + F^i(\mathbf{r}, t). \quad (6.3)$$

A useful shorthand is to think of this distribution as a vector in a Hilbert space and write $\mathbf{F} = \mathbf{F}^c + \mathbf{F}^d + \mathbf{F}^b + \mathbf{F}^i$.

If the drug must be internalized to be cytotoxic, only $\mathbf{F}^i$ contributes to the probability of tumor control, and the test statistic for patient j is given by $\tau = T(\mathbf{F}_j^i)^*$. The TOC analog of (6.2), for a single patient j rather than a class, becomes

$$Pr(TC|M_j, j) = Pr(\tau > \tau_0|M_j, j) = \int_{\tau_0}^{\infty} d\tau \quad pr(\tau|M_j, j) = \int_{\tau_0}^{\infty} d\tau \int d\mathbf{F}_j^i \quad pr(\tau|\mathbf{F}_j^i) \quad pr(\mathbf{F}_j^i|M_j, j). \quad (6.4)$$

In both ROC analysis and TOC analysis, linear discriminants play a key role. For digital images with N elements, the general linear discriminant is a scalar product of the form

$T(\mathbf{g}) = \mathbf{w}^t \mathbf{g} = \sum_{n=1}^N w_n g_n$, where the *template* $\mathbf{w}$ is a vector the same size as the image. Linear discriminants are often good models of human observers, and they describe the ideal observer if the data statistics are multivariate normal and the signal to be detected is weak.

In TOC analysis for chemotherapy, the general linear discriminant is also a scalar product, but now in terms of continuous variables:

$$T(\mathbf{F}_j^i) = \int_0^{\infty} dt \int_V d^3r \quad F_j^i(\mathbf{r}, t) s(\mathbf{r}, t), \quad (6.5)$$

where V is the volume of the tumor. The template $s(\mathbf{r}, t)$ in this case can be interpreted as the *sensitivity* of the tumor cells at point $\mathbf{r}$ and time t to the intracellular component of the drug; the spatial variation of $s(\mathbf{r}, t)$ is the relevant description of the heterogeneity of the response, and the temporal variation over a long time scale is descriptive of evolving sensitivity to the drug.

An important special case of linear discriminants in both ROC and TOC is where the template is a constant over some spatial region and temporally. In image-quality studies, this case is called the *non-prewhitening matched filter*, and for TOC, setting $s(\mathbf{r}, t)$ to the constant $1/V$ yields

$$T(\mathbf{F}_j^i) = \frac{1}{V} \int_0^{\infty} dt \int_V d^3r \quad F_j^i(\mathbf{r}, t). \quad (6.6)$$

*For chemotherapeutic agents that are effective without internalization and for targeted radionuclide therapy, $\mathbf{F}^i$ should be replaced by $\mathbf{F}^i + \mathbf{F}^b$ in what follows

Dimensionally, this discriminant is a concentration times a time, and it is a familiar construct in the chemotherapy literature, referred to there as AUC, meaning the area under a curve of drug concentration vs. time. In clinical oncology, however, the concentration is determined from blood samples at a sequence of times, because that is all that can be measured directly on a patient or experimental animal. We refer to this common clinical metric as *serum AUC*, or *sAUC* for short, and in (6.6) we are defining the *intracellular AUC*, denoted *iAUC*. For patient j , *iAUC* is a monotonically increasing but not necessarily linear function of M_j , so we write it as $iAUC_j(M_j)$.

Because linear discriminants are sums or integrals of a large number of more-or-less independent random variables, they tend to have univariate normal probability density functions, and the integral over τ in (6.2) or (6.4) can be expressed in terms of an error function, $\text{erf}(\cdot)$. For chemotherapy with $\tau = iAUC_j(M_j)$ as the test statistic for patient j , (6.4) becomes

$$\Pr(TC|M_j, j) = \Pr(iAUC_j(M_j) > \tau_0) = \frac{1}{2} + \frac{1}{2} \text{erf}\left(\frac{\tau - \tau_0}{\sqrt{2}\sigma}\right). \quad (6.7)$$

Since $\text{erf}(0) = 0$, we can interpret τ_0 as the value of *iAUC* for which $\Pr(TC) = \frac{1}{2}$, and the parameter σ determines the steepness of the curve of $\Pr(TC)$ vs. *iAUC* through this point.

6.2 Estimation of $\Pr(TC)$ from image data

The free parameters in (6.7), τ_0 and σ , are characteristics of the tumor type and the drug, and in principle they can be determined from databases or *in vitro* studies; an analytic approach to predicting cell response from *in vitro* data is given by Gardner.³⁶

The patient-specific part of (6.7) is $iAUC_j(M_j)$, which we have to estimate from the dynamic images acquired in the radiotracer study on patient j . We denote the resulting estimated tumor-control probability as $\hat{\Pr}(TC|\mathbf{G}_j, M_j, j)$, which is a posterior probability in the sense of this paper because it is computed from the image data that distinguish the posterior ensemble from the prior ensemble.

As a starting point for discussing the estimation, we can go back to the tracer-stage concentration expression in (4.8). Within a constant, the left-hand side is the total activity per unit volume in the tumor as a function of position and time, which is the object being imaged in the tracer study. Within the limitations imposed by the spatial and temporal resolutions of the imaging system and the duration of the scan, $f_j(\mathbf{r}, t)$ is directly observed in the image data $\mathbf{G}_j$. Other information that can be obtained from the images includes the gross anatomy of the tumor and surrounding tissues and measures of the heterogeneity of the tracer distribution at various time points.

Following the ground-breaking work of Wittrup, Schmidt, Orcutt, Thurber and Weissleder,³⁷⁻⁴⁰ we assume that the image data $\mathbf{G}_j$ are used to estimate a set of K drug-delivery parameters, Θ_k ; $k = 1; \dots K$; these parameters can include tumor vascularity, capillary permeability, diffusion coefficient, receptor density, binding potential,

internalization rate and residualization rate. For patient j , we can assemble these parameters into a $K \times 1$ vector denoted Θ_j .

With this notation, the posterior probability we need is $\Pr(TC|\Theta_j, M_j, j)$. The patient indicator j still appears because, in addition to Θ_j and M_j , we can also account for other patient-specific factors such as genomic data; blood tests; size and grade of the tumor, and clinical history.

We do not know the true Θ_j for a particular patient, so we must estimate it from the image data $\mathbf{G}_j$ in order to compute $\Pr(TC|\Theta_j, M_j, j)$. The estimates of Θ_j are denoted $\hat{\Theta}_j$, and the resulting estimate of the probability of tumor control is denoted $\hat{Pr}(TC|\Theta_j, M_j, j)$.

By the definition of conditional probabilities, we can write

$$\hat{Pr}(TC|\Theta_j, M_j, j) = \int d\hat{\Theta}_j \int d\mathbf{G}_j \Pr(TC|\hat{\Theta}_j, M_j, j) \Pr(\hat{\Theta}_j|\mathbf{G}_j) \Pr(\mathbf{G}_j|\Theta_j, j). \quad (6.8)$$

where $\Pr(\cdot)$ denotes a probability density function (PDF). We do not need the extra conditioning on j in $\Pr(\hat{\Theta}_j|\mathbf{G}_j)$ because the estimation process is a direct mapping from $\mathbf{G}_j$ to $\hat{\Theta}_j$ without using the genomic and clinical information discussed above. The j in $\Pr(\mathbf{G}_j|\Theta_j, j)$ is still needed to account for the patient's anatomy and other factors that might influence the image data; these factors are called *nuisance parameters*,^{1,2} defined as quantities that affect the data, and hence the estimate, but are not of direct interest for the estimation problem at hand.

We can also recognize that

$$\int d\mathbf{G}_j \Pr(\hat{\Theta}_j|\mathbf{G}_j) \Pr(\mathbf{G}_j|\Theta_j, j) = \Pr(\hat{\Theta}_j|\Theta_j, j), \quad (6.9)$$

so that

$$\hat{Pr}(TC|\Theta_j, M_j, j) = \int d\hat{\Theta}_j \Pr(TC|\hat{\Theta}_j, M_j, j) \Pr(\hat{\Theta}_j|\Theta_j, j). \quad (6.10)$$

This form is particularly useful if we assume that $\hat{\Theta}_j$ is obtained from $\mathbf{G}_j$ specifically by maximum-likelihood estimation (MLE),^{1,2} in which case $\Pr(\hat{\Theta}_j|\Theta_j, j)$ is a simple multivariate Gaussian, at least asymptotically, and (6.10) becomes a K -dimensional convolution. The interpretation of (6.10) is that $\Pr(TC|\Theta_j, M_j, j)$ is the probability of tumor control that we would get if we knew the drug-delivery parameters exactly, and the estimated probability is that hypothetical probability after consideration of the uncertainties of estimating the delivery parameters from the image data.

With the estimates $\hat{\Theta}_j$ and knowledge of the tumor anatomy from the images, we want to estimate the intracellular drug distribution $F_j^i(\mathbf{r}, t)$ and hence to estimate $iAUC_j(M_j)$. The simplest approach is to neglect receptor saturation and assume that $F_j^i(\mathbf{r}, t)$ is just the

intracellular radiotracer distribution, $f_j^i(\mathbf{r}, t)$, scaled by M_j/m_j , where m_j is the administered mass of the radiotracer. Receptor saturation makes the drug-delivery equations nonlinear, but in principle we can use the estimated parameters and knowledge of the tumor anatomy from the images to perform Monte Carlo simulations to estimate $iAUC_j(M_j)$. The estimated posterior probability of tumor control then follows from (6.7) with the parameters Θ_0 and σ known from other sources.

The similarity of this procedure to TOC analysis in radiation therapy should not be overlooked. In that case, the “data” to be read by the tumor is the distribution of absorbed radiation dose, $d(\mathbf{r}, t)$, and it is not necessary to distinguish total and intracellular dose. Estimates of probabilities of tumor control and normal-tissue complications are based on linear discriminants, referred to as total dose, equivalent uniform dose or effective dose, all of which are linear functionals of $d(\mathbf{r}, t)$. The response models are all based on univariate cumulative distribution functions as in (6.2) and (6.4), and often they assume univariate normals that lead to exactly the same expression as in (6.7). Tables of the free parameters, like our Θ_0 and σ , have been compiled for many kinds of tumor and many different adverse responses in normal tissues.^{20,21}

6.3 Comments on clinical applicability of iAUC

Though more general treatments are possible and may be needed, (6.7) and (6.10) depend on the premise that $iAUC$ is a good predictor of tumor response. Cell-cycle-independent drugs such as alkylating agents (cyclophosphamide, cisplatin, etc.) may be the best case for this hypothesis, but there are some important caveats:

1. Cell-cycle specific drugs such as the antimetabolites (5-FU, methotrexate, gemcitabine, etc.) tend to reach a dose plateau beyond which higher doses aren't more effective. Integrating intracellular AUC over a long-enough time to cover multiple cell-cycles might get around this problem (recognizing the cells in the tumor will be at different points in the cycle at any one time).
2. Most chemotherapy is given as combination therapy rather than monotherapy (although there are important exceptions). Combining cell-cycle-independent and -dependent drugs is probably the most common regimen, and the resulting response should be greater than the sum of the individual responses. The combination could be difficult to model, although the premise of AUC over an entire chemotherapy cycle might still hold.
3. Multiple clones in a tumor may respond very differently to different chemotherapy agents. For example, ER+ cells in breast cancer may have a rapid and durable response to anti-estrogens, which will do nothing to ER- cells in the same tumor. As different clones are selected as a consequence of therapy, new agents (in this example, cytotoxic chemotherapy) would have to be modeled; anti-hormonal therapy and chemotherapy would not be given together at the outset, since the chemotherapy would blunt the response to anti-hormonal therapy.

Another important clinical issue regards the route of administration of the therapeutic drug. Though intravenous (IV) administration is by far the most common route, there may be large

advantages in intraperitoneal (IP) administration for abdominal tumors.⁴¹⁻⁴⁵ The formalism of this paper should be immediately applicable to IP administration, and *iAUC* should still be a useful predictor.

7. SUMMARY AND CONCLUSIONS

The new material in this paper is in Secs. 5 and 6, where we apply concepts from image science to the analysis and optimization of cancer therapy.

In Sec. 5, we discuss the conceptual and mathematical dilemma confronting all forms of personalized medicine. If diagnostic or therapeutic efficacy is defined in terms of average outcome over a population (ensemble) of patients, what does it mean to optimize the process for an individual, and how do we validate the optimization? The answer, taken from the literature on adaptive imaging,^{34,35} is to acquire supplementary data (often images) on a particular patient and use them to refine the statistical description of the population under study. The resulting posterior ensemble is defined as the subset of all patients in the prior ensemble who could have given the same supplementary data within the uncertainty of the measurement. The suggested (and possibly only) approach to rigorous personalized medicine is to optimize the therapy or diagnostic test for the posterior ensemble, but to test the usefulness of the optimization with conventional clinical trials or other assessment based on the prior ensemble.

Following this paradigm requires mathematical models and statistical estimation methods that allow us to make statements about the posterior probabilities and the extent to which the posterior ensemble is “smaller” than the prior ensemble, in the sense of including less patient-to-patient variability.

The methodology for this purpose is borrowed from statistical decision theory, especially as applied to objective, task-based, assessment of image quality.¹ The essential steps are sketched in Sec. 6 for the specific case of personalized chemotherapy. We treat the tumor as an observer reading a data set and responding by continuing to grow or by stopping or shrinking. Without loss of generality, the response can be construed as computing a scalar-valued functional of the data, called a test statistic, and comparing it to a threshold. The loss of generality comes from an assumption frequently made in many different fields that this test statistic is a linear functional of the data, and we are led to discuss linear discriminants.

In chemotherapy, the data set in question is the distribution of the drug within the tumor, and if the drug is cytotoxic only when it is incorporated into the cytoplasm, the linear discriminant must be a weighted integral of the intracellular distribution of the drug. The simplest weighting factor is a constant, and in this case the discriminant function is the area under a curve of average intracellular drug concentration vs. time, which we denote as *iAUC*. Methods of estimating *iAUC* from imaging data on a particular patient are discussed, and a simple final expression for probability of tumor control for the posterior ensemble defined by that patient is derived in Sec. 6.1. The expression depends on two free parameters, which must be determined by clinical or laboratory studies on the prior ensemble.

Many open questions remain. An immediate issue related to data acquisition is that the time course of the distribution of the radiotracer can extend over hours or days, so a radioisotope with a long half-life is required. PET isotopes Zr-89 (half-life 78.4 hr) and I-124 (100 hr) and SPECT isotope In-111m (67 hr) have been suggested for labeling antibodies, but there are logistical difficulties in acquiring multiple images of a patient over this time scale. The optimum choice of number and timing of the imaging sessions can be determined by use of the Fisher information matrix and Cramer-Rao bound for the estimation of iAUC.¹

Once the imaging data are acquired, the recommended next step is to perform maximum-likelihood estimation of the drug-delivery parameters. Accurate likelihood functions with careful attention to null functions and nuisance parameters are needed for this purpose.

The parameters estimated from the radiotracer study provide information about the distribution of the drug only when it is administered at trace concentrations so that the transport equations are linear. New analytic methods involving nonlinear differential equations or Monte Carlo simulation are needed to get the distribution at higher concentrations where receptor saturation can occur.

Considerable research is also needed to develop experimental and analytic approaches to determining the tumor-response parameters Θ_0 and σ , introduced in Sec. 6. It is not uncommon for tumor specimens from a patient to be used in chemotherapy sensitivity/resistance assays for multiple drugs; quantitative results from these assays could be used to get personalized estimates of the response parameters,³⁶ but many details must be worked out.

Animal and clinical studies are clearly needed to validate this whole approach, and there are many variants and refinements of the methodology and many possible mathematical models from which to choose. The ultimate goal is to demonstrate that personalized chemotherapy with precision estimation of patient-specific parameters for drug delivery and tumor response results in improved clinical outcomes, as quantified by an increase in area under the TOC curve. Useful intermediate steps are to quantify the precision and accuracy of the estimates of the drug-delivery parameters; to validate the response models and establish values for the parameters that occur in them, and to either validate iAUC as the appropriate test statistic or to consider more general linear or nonlinear formulations.

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Figure 1.

Schematic Therapy Operating Characteristic curves for two treatment plans on the same patient. The plan corresponding to the upper curve will give a higher probability of tumor control for a given probability of normal-tissue complication; different complications would give different TOC curves.

Figure 2.

Concentration of a monoclonal antibody as a function of time following an impulse injection at $t = 0$ (i.e., $s(\mathbf{r}, t) \propto \delta(t)$). Spatially, the impulse source was a thin spherical shell surrounding the observation point, but except for a scale factor on the ordinate, the same result would be obtained for injection at a point.

	Adaptive imaging	Personalized therapy
Prior ensemble	Set of all patients presenting for a given diagnostic study with a given modality	Set of all patients with a given cancer and undergoing therapy with a given drug
Posterior ensemble	Set of all patients in prior ensemble and consistent with initial <i>static</i> imaging studies on a particular patient	Set of all patients in prior ensemble and consistent with initial <i>dynamic</i> imaging studies on a particular patient

Figure 3.
Paradigm for adaptive imaging and personalized therapy