Acidose metabólica leve. Possível causa do aumento da sobrevida de pacientes com câncer renal metastático pós nefrectomia

The Possible Role of Postoperative Azotemia in Enhanced Survival of Patients with Metastatic Renal Cancer after Cytoreductive Nephrectomy


Abstract

Cytoreductive nephrectomy prior to systemic therapy significantly increases survival in patients with metastatic renal cancer. This result is generally ascribed to the benefits of resection of the primary tumor including reduction of tumor burden, removal of a source for growth factors and metastases, and enhanced immune response. On the basis of mathematical models of tumor invasion, we propose that the observed effects of cytoreductive nephrectomy may be caused by resection of the kidney rather than the cancer. The models predict that the graded metabolic acidosis associated with mild renal failure after unilateral nephrectomy may alter the dynamics of the tumor-host interface sufficiently to reduce and even reverse the rate of invasion. A review of patient data from the surgical arm of the Southwest Oncology Group (SWOG) 8949 trial demonstrates significantly improved survival in patients who experienced postoperative increase in blood urea nitrogen (BUN) and creatinine compared with those who did not (17-month survival versus 4-month survival; \( P = 0.0007 \)). This is generally consistent with the predictions of the mathematical models. If confirmed, these results suggest novel and broadly applicable tumor therapies.

INTRODUCTION

The clinical benefit of cytoreductive nephrectomy in the treatment of metastatic renal cancer has been extensively studied. “Spontaneous” regression of metastatic lesions in the absence of systemic therapy has been demonstrated in 0.4–6% of patients \( 1, 2, 3, 4 \) after surgical resection of the primary tumor. Two recent clinical trials have found that cytoreductive nephrectomy prolongs the survival in patients treated with IL \( 3 \)-2 and IFN \( \alpha -2b \) \( 5, 6 \) despite similar response rates in the surgical and nonsurgical arms. Multivariate
analysis in a large series of patients with metastatic renal cancer receiving a variety of therapies demonstrated the history of nephrectomy to be the sole significant parameter associated with duration of survival (7). This has lead to recommendations that cytoreductive nephrectomy before immunotherapy be considered standard treatment for metastatic renal cell carcinoma in patients who are suitable candidates (8).

The mechanisms for the observed effect of cytoreductive nephrectomy on survival are unknown. Most authors speculate that the benefits are from resection of the primary tumor and related to reduction of the total tumor burden, loss of a source for tumor growth promoters and later metastases, and removal of a trap for trafficking lymphocytes (5, 6).

Two of us (R. A. G. and E. T. G.) have proposed a mathematical model of malignant invasion based on tumor–induced toxicity in adjacent normal tissue (9, 10). Although the microenvironment in malignant tumors is spatially and temporally heterogeneous, the pH$_e$ is consistently measured to be more acidic than that of normal tissue, presumably as a consequence of increased glycolytic metabolism and acid excretion.

The mathematical models demonstrate this tumor–induced perturbation in the microenvironment results in the preferential growth of transformed cells, which are more tolerant of harsh conditions including acidic pH, than are nontransformed cells (11). Using a diffusion–reaction model, we have demonstrated that these acidic regions will produce a proton gradient extending from the tumor edge into adjacent normal tissue (9, 10). An acidic pH$_e$ induces apoptosis via a p53–dependent pathway (12) initiated by increasing caspase activity (13). This produces a peritumoral ring of dead and dying cells into which the still viable malignant cells invade (9). Microenvironmental acidification also stimulates the release of proteolytic enzymes, causing the degradation of the extracellular matrix (14), the release of IL–8 and VEGF inducing angiogenesis (15, 16), and inhibition of the immune response (17). All of these effects serve to enhance tumor invasion.

In the initial description of this model (9), we demonstrated that the solution to the state equations that yielding invasive tumor growth was only conditionally stable. That is, perturbations in critical parameters could result in evolution of the system to a new steady state, including the null solution (i.e., complete tumor regression). This suggested that novel therapies, directed toward the critical parameters of the system, could be developed. In this report, we investigate one possible approach: alteration of the systemic pH sufficiently to perturb the pH$_e$ in the tumor and peritumoral normal tissues. We find, using stability analysis of the fixed–point solutions of the state equations that govern the tumor–host interface, that the invasive cancer fixed point may be destabilized by an increase (or decrease) in the serum H$^+$ concentrations. The subsequent drift of the system to the null fixed–point solution will manifest clinically as an apparent spontaneous regression of the cancer. Numerical simulations based on these models demonstrate perturbations in the tumor microenvironment will decrease the speed with which the tumor edge propagates into normal tissue.

This leads to the hypothesis that the clinical benefit observed in patients with metastatic renal cancer after cytoreductive nephrectomy may be caused by resection of the kidney rather than the primary tumor. Briefly, we note that cytoreductive nephrectomy will result in mild renal dysfunction attributable to loss of functioning nephrons in the resected kidney. Mild renal failure (a mean increase in BUN and creatinine of 18 to 20% in the S8949 study)
is typically associated with a graded metabolic acidosis (18, 19, 20). We propose that this systemic pH perturbation, although relatively small, may alter the microenvironment in the tumor and peritumoral normal tissue sufficiently to reduce tumor growth rate and prolong survival. Our theoretical mechanism for this effect is as follows: the decrease in systemic pH will inhibit the removal of acid from the tumor because the flow of protons from the interstitial space into the tumor vasculature (and buffers in the opposite direction) is dependent on the H+ gradient across the vessel wall. Decreasing the systemic pH diminishes this gradient, which results in further acidification of the tumor pH. In some or all of the regions of the tumor, the increased H+ concentration may exceed the tolerance of tumor cells, which results in necrosis, paradoxical reduction of the peritumoral acid gradients, and slowing or even reversal of the tumor invasion.

This hypothesis is supported by a demonstration of a correlation between post-nephrectomy renal dysfunction and enhanced survival in patients with metastatic renal cancer.

**METHODS**

Dynamical Systems Model of Systemic Acidification and Alkalization.

The complete set of governing equations for the tumor host interface and the stability analysis of those equations have been published previously (9). Here we examine only the potential effect of alterations of the systemic pH on the stability of the fixed-point solution that yields invasive cancer. The simplest possible dynamical model of the process of systemic acidification or alkalinization and their effects on tumor growth is one in which tumor cells obey a logistic growth law and suffer either from extreme acidification or alkalization. The latter death term must saturate at both high and low pH and should go to zero at the optimal pH for tumor growth. An obvious candidate function capturing these responses is the ratio of quadratic polynomials:

\[ f(H) = \frac{(H - H_{\text{opt}})^2}{H^2 + bH + H_{\text{cap}}^2} \]

where \( H \) is the H+ ion concentration expressed as a molarity (M). This function has the desirable properties that \( f(H_{\text{opt}}) = 0 \), \( f(0) = 1 \), and \( f(H \to \infty) = 1 \). The parameter \( b \) in equation (A) sets the width of the hospitable zone. If \( H_{1/2} > H_{\text{opt}} \) is the half-maximum point on the acidic side, then \( b = H_{1/2} [1 - 4H_{\text{opt}}/H_{1/2} + (H_{\text{opt}}/H_{1/2})^2] \) such that \( f(H_{1/2}) = 1/2 \). The equation governing the evolution of tumor thus becomes

\[
\frac{dT}{dt} = r_T T \left( 1 - \frac{T}{K_T} \right) - d_T f(H) T
\]

where \( T \) is the concentration of tumor cells (cells/cm³), \( r_T \) is the tumor growth rate (1/s), \( K_T \) is the tumor carrying capacity (cells/cm³), and \( d_T \) is the maximum death rate (1/s) for either extreme acidification or alkalization.

The H+ ion production rate is determined by the tumor concentration and the degree of local vascularization:

\[
\frac{dH}{dt} = r_H T - d_H (H - H_s)
\]

where \( r_H \) is the H+ ion production rate by tumor cells (M·cm³)/(cell·s), \( H_s \) is the serum H+ ion concentration, and \( d_H \) is the rate of removal (or addition) of H+ ions if the local H+ ion concentration is greater (or less) than that within the serum. Typically, \( d_H = \alpha \rho \), where \( \alpha \) is the blood vessel areal density (1/cm) and \( \rho \) is the vessel permeability (cm/s) leaving \( d_H \) with units of 1/s; however, it could also be viewed as having contributions because of buffering capacity.
Acidification is achieved if the parameter $H_s$ substantially exceeds $10^{-7.4}$ M, and alkalinization occurs when it is substantially less than $10^{-7.4}$ M.

The variable transformations $\tau = T/K, \ h = H/H_{opt}$, and $s = r_t$ can be used to put equations (A) and (B) into dimensionless form:

$$
\frac{d\tau}{ds} = \tau(1 - \tau) - \delta_h(h - h_0)
$$

where $\delta_r = \delta_t/r_t$, $\rho_h = r_K/(nH_{opt})$, $h = H/H_{opt}$, and $\delta_h = \delta_t/r_t$ are four dimensionless parameters that control the dynamics of the system. The equations in (D) have two fixed points [(i.e., $(\tau, h)$ values at which $d\tau/ds = 0$ and $dh/ds = 0$), one where $(\tau = 0, h = h_0)$ and the other where $(\tau > 0, h > h_0)$. The detailed form of the latter is quite complicated, being the solution of a cubic polynomial. Nevertheless, the conditions required to render the $(\tau = 0, h = h_0)$ fixed point stable can be determined by performing a linear stability analysis. In this way, it is found that if

$$
\delta_r h_{1/2}(h_0 - 1)^2 > 1
$$

then the absence of tumor is a stable state. If $\delta_r > 1$, condition (E) is satisfied provided that either

$$
\frac{1 + 2h_{1/2}(\delta_r - 2) + h_{1/2}^2 + (h_{1/2} - 1)\sqrt{h_{1/2}^2 + h_{1/2}(4\delta_r - 6) + 1}}{2(\delta_r - 1)h_{1/2}} \equiv h_0^+ \\
\frac{1 + 2h_{1/2}(\delta_r - 2) + h_{1/2}^2 - (h_{1/2} - 1)\sqrt{h_{1/2}^2 + h_{1/2}(4\delta_r - 6) + 1}}{2(\delta_r - 1)h_{1/2}} \equiv h_0^-
$$

Condition (F) corresponds to a state of acidosis and (G) to one of alkalosis. As $\delta_r \rightarrow 1^+$, the unstable gap between $h_0^+$ and $h_0^-$ diverges so that the $(\tau = 0, h = h_0)$ fixed point becomes unconditionally unstable $\forall \delta_r \leq 1$, i.e., the system will evolve to the $(\tau > 0, h > h_0)$ state. Fig. 1 is an $h_s-\delta_r$ stability diagram (black, stable; white, unstable) for the $(\tau = 0, h = h_0)$ fixed point with $h_{1/2} = 5/2$.

**Fig. 1.**

An $h_s-\delta_r$ stability diagram (black, stable; white, unstable). For the $\tau = 0, h = h_0$ fixed point with $h_{1/2} = 5/2$. The tumor solution to the governing equation (see Text) is stable only in the white regions of the diaphragm. Alteration of the systemic pH in a tumor-bearing host
could move the system across the threshold resulting in destabilization of the “tumor” fixed point and stabilization of the null fixed point \( (\tau = 0) \). The transition of the system from one stable state to the other would manifest clinically as a spontaneous regression of the tumor.

The simple model given by equations (B) and (C) demonstrates clearly that tumor can be suppressed by either systemic alkalization or acidification provided that \( \delta > \delta \) (\( \delta > 1 \)). In other words, modification of the systemic pH may, under some circumstances, destabilize the “tumor solution” of the state equations resulting in migration of the system to the null solution. This would manifest clinically as an apparently spontaneous regression of the tumor.

One inherent weakness in the model is that the serum H\(^+\) ion concentration required for sufficient acidification to suppress tumor is always greater than the optimal H\(^+\) ion concentration for tumor growth. This is found to be because the conditions in equations (F) and (G) do not depend on \( \rho \) or \( \delta \), clearly an unphysical result.

More complicated diffusion–reaction models that the authors have devised (involving competition between tumor and host cells and density dependent diffusion) do not suffer from this deficiency, and more modest acidification can lead to a reduction in the tumor growth rate, if not a complete regression, consistent with the cellular automaton results described in the next section.

**Cellular Automaton Model of Systemic Acidification.**

In a recent article (10), the authors described a hybrid cellular automaton model used to simulate early tumor growth and to examine the roles of host–tissue vascular density and tumor metabolism on the ability of a small number of monoclonal transformed cells to develop into an invasive tumor. The model incorporated normal cells, tumor cells, necrotic or empty space, and a random network of native microvessels as components of a cellular automaton state vector. Diffusion of glucose and H\(^+\) ions (the latter largely resulting from the excessive reliance of the tumor on anaerobic metabolism) to and from the microvessels, and their utilization or production by cells, was modeled through the solution of differential equations. In this way, the cells and microvessels affect the extracellular concentrations of glucose and H\(^+\) which, in turn, affect the evolution of the automaton.

Computer simulations of the model (10) demonstrated that: (a) high tumor H\(^+\) ion production is favorable for tumor growth and invasion; however, for every H\(^+\) ion production rate, there exists a range of optimal microvessel densities (leading to a local pH favorable to tumor but not to normal cells) for which growth and invasion is most effective; (b) at vascular densities below this range, both tumor and normal cells die because of excessively low pH; and (c) for vascular densities above the optimal range, the microvessel network is highly efficient at removing acid and, therefore, the tumor cells lose their advantage over normal cells gained by high local H\(^+\) concentration. It was also observed that a sharp transition (analogous to that of the adenoma–carcinoma sequence) between states of initial tumor confinement and efficient invasiveness occurs when, for a particular microvessel density, H\(^+\) production reaches a critical value. The tumor growth rate continues to increases with H\(^+\) production until an optimal value is reached. Beyond this optimal H\(^+\) production, the tumor growth rate declines.
Of the 20–odd quantities parameterizing this cellular automaton model, one is serum pH. The partial differential equation governing acid distribution must satisfy a boundary condition at the microvessel walls requiring the acid flux across the wall to be proportional to the acid concentration difference between that in the serum and that just outside the microvessel. The sign of this concentration difference determines the direction of acid (and, thus, dissociated \( \text{H}^+ \)) flux. In all of the simulations described in Ref. 10, the serum pH was taken to be the normal value of 7.4.

A natural question as to the effect of serum pH on tumor growth arises and, particularly in the context of this paper, the effect on tumor metastases. It is reasonable to assume, at least within the framework of the acid–mediated tumor invasion hypothesis, that metastatic tumors are comprised of a clone with an optimal acid production phenotype. To test the effects of systemic acidification on such metastases, we selected a 200×200 automaton with a typical microvessel density (0.08 corresponding to microvessel areal density of 160.0/cm), setting the tumor–acid production rate to the corresponding optimal value (8.0 \( \times 10^{-5} \text{ mm/s} \)) for growth. The automaton was then seeded with a small (100-μm) tumor whose growth rate was monitored for 50 generations. The serum pH was then systematically lowered from 7.4 to 7.0 in increments of 0.02, with each run averaged over 20 different random microvessel configurations. In Fig. 2, it is apparent that tumor growth rate is substantially suppressed with increasing systemic acidification. The error bars on data points indicate SE.

![Fig. 2.](image)

Tumor growth rate is shown to slow with systemic acidosis using cellular automaton computer simulations as outlined in the Text. The \( Y \) axis represents the change in tumor diameter and, thus, underestimates the reduction in the growth rate of tumor volume.

**Clinical Methods.**

A retrospective review of patient records from the cytoreductive nephrectomy arm of the SWOG 8949 study was performed. The details of this study have been reported elsewhere (6). Briefly, all of the enrolled patients with metastatic renal cancer were treated with IFN \( \alpha-2b \). Eligibility criteria included histologically confirmed diagnosis of metastatic renal...
cancer, a primary tumor that was considered resectable by the attending physician, a performance status of 0 or 1 according to the SWOG criteria, serum bilirubin no higher than three times the institutional limits of normal, and a serum creatinine level of no more than 3.0 mg/dl (265 μmol/liter). Patients were excluded if they had received prior treatment with chemotherapy, hormonal therapy, IFN, IL–2, lymphocyte–activated killer cells, or other biological–response modifiers. Before therapy with IFN α–2b, one–half of the patients were randomly assigned to receive cytoreductive nephrectomy and the others had no surgery. The results demonstrated a statistically significant increase in length of survival in the surgery arm compared with those not receiving surgery independent of performance status, metastatic site, and the response to IFN α–2b (6).

A total of 95 patients in the SWOG 8949 study underwent a cytoreductive nephrectomy and at least one treatment with IFN α–2b. From these charts, pre– and postsurgical values of BUN were obtained in 87 patients and creatinine in 85. In each case, the BUN and creatinine at the time of enrollment were used as the presurgery values, and the measurements on the day of first treatment with IFN α–2b were considered the postsurgery values. Patient demographics as well as length of survival and progression–free survival were available through the study database.

Proportional hazards regression models were used to evaluate the effect of changes in BUN and creatinine after surgery on survival and progression–free survival. Quartiles were identified for changes in BUN and creatinine in the sample, and indicators for quartiles 2, 3, and 4 were placed in the respective regression model with quartile 1 being the reference value. Additionally, gender, age, and body mass index at study entry were included in the model. As from the Wald χ² test of each quartile relative to quartile 1 are reported in Table 1. Survival time is defined as date of nephrectomy to date of death or last contact, and progression–free survival is defined from the date of nephrectomy to the date of progression or death or date of last contact (whichever occurs first).

Results

After cytoreductive nephrectomy, the mean increase in BUN was 3 (range, −14–43), and the mean increase in creatinine was 0.2 (range, −0.7–3.3). The mean fractional change (postoperative value minus preoperative value divided by the preoperative value) was 0.18 for BUN and 0.22 for creatinine. Patient demographics were similar (data not shown) between those who developed postoperative azotemia compared with those who did not
except that the former group was more likely to have a baseline performance status of 0 (70 versus 50%).

As demonstrated in Table 1 and Fig. 3, survival and progression-free survival were significantly better in those patients who developed renal dysfunction after cytoreductive nephrectomy compared with those who did not (17–month mean survival in the renal failure groups versus 4–month survival in the non–renal failure group). As predicted by the mathematical models, those patients who did not develop postoperative renal failure demonstrated survival essentially identical to the nonoperative arm of the study. A definite correlation between the degree of renal failure and survival could not be obtained, although there was a general trend of prolongation of survival with an increasing percentage of change in BUN and creatinine in the second and third quartiles. Interestingly, this trend reversed in patients with the highest percentage change of BUN and creatinine (fourth quartile), possibly because of the addition of deleterious survival effects in more severe renal failure.

![Fig. 3.](image)

**Fig. 3.**

Actuarial survival among patients receiving cytoreductive nephrectomy in SWOG 8949 according to changes in the postsurgical creatinine. ———, patients with no decline in renal function. ———, all of the patients with postoperative increases in BUN and creatinine. The median survival for patients with no postoperative renal dysfunction was 4 months but was 17 months for those with dysfunction. 0, no postoperative renal dysfunction; 1, some measurable increase in creatinine.

We did not find any example of spontaneous tumor regression after nephrectomy in the patients enrolled in the SWOG 8949 study, although several patients demonstrated prolonged survival (see Fig. 3).

**DISCUSSION**

Our retrospective analysis supports the hypothesis that at least some of the clinical benefits from cytoreductive nephrectomy in patients with metastatic renal cancer may be related to the removal of functioning nephrons. This hypothesis emerged from mathematical models of the tumor–host interface that demonstrate tumor-generated acidification of adjacent normal tissue is sufficient to produce invasive behavior. We have previously noted
that the solution to the state equations that yields invasive tumor growth is only conditionally stable (9). Thus, manipulation of critical parameters could result in perturbations in the system ranging from the slowing of tumor growth to rapid evolution to a new steady state in which no tumor is present. The former would manifest clinically as a slowing in the tumor growth rate and presumably a corresponding increase in the length of survival, whereas the latter would produce an apparent spontaneous regression of the cancer.

One such critical parameter is the pH within the tumor. We hypothesized that alterations in systemic pH could perturb the tumor pH sufficiently to favorably alter the tumor growth rates. This occurs because the acid concentration in the tumor extracellular space is critically dependent on the intratumoral blood flow for buffering and evacuation. The diffusion of acid from the tumor interstitial space into the blood vessels (and buffers in the opposite direction) will be dependent on the pH gradient across the vessel wall. A reduction of serum pH decreases this gradient resulting in decrease flow and, thus, accumulation of acid in the tumor. This decline in pH, may become sufficient to exceed the tolerance of tumor cells, which would result in necrosis.

Here, we present an analysis of the mathematical models demonstrating that perturbations in the tumor microenvironment caused by clinically achievable alterations in systemic pH are sufficient to produce a significant reduction in the velocity of propagation of the tumor edge into normal adjacent tissue and even a spontaneous regression of the cancer. Presumably, this decreased growth rate results in improved patient survival.

Although seemingly paradoxical, the mathematical models demonstrate that systemic acidification will result in decreased tumor invasiveness because of a self-poisoning effect. That is, the tumor cells undergo necrosis because of the additive effects of their own acid production and decreased acid removal through tumor vasculature caused by reduction in the pH gradient across the vessel walls discussed above. As demonstrated in the mathematical models, this phenomenon will usually result in some decrease in the propagation velocity of the tumor edge. However, in some cases, the effect may be sufficient to destabilize the solution of the state equations. The resulting shift to a new fixed point solution will produce total cancer cell death and an apparent spontaneous regression of the clinical tumor.

Our retrospective analysis of patients receiving cytoreductive nephrectomy before systemic treatment with IFN α–2b demonstrates a significant survival benefit in patients with postoperative renal dysfunction. This finding is consistent with our hypothesis that at least some of the observed clinical effects of cytoreductive nephrectomy are caused by the removal of the kidney rather than of the tumor. Unfortunately, no additional data were available in the SWOG 8949 study regarding the systemic effects of the post-nephrectomy changes in renal function. As a result, we cannot determine whether the mechanism by which mild renal failure improves survival is metabolic acidosis as predicted by the mathematical models. Furthermore, we cannot exclude the possibility that differences in patient demographics between the renal-failure and non-renal-failure groups contribute significantly to the observed effects.

Systemic acidification has, in fact, been demonstrated to reduce in vivo tumor growth (21, 22, 23). Furthermore, scattered clinical reports have demonstrated spontaneous regression
of cancers in the presence of severe systemic acidosis after, for example, ureterosigmoidostomy (24).

The present study clearly has multiple limitations including the retrospective nature of the analysis, the absence of important data such as measurements of systemic pH and electrolytes, and the possibility of other clinical factors contributing to the results. However, the implications of the results, if confirmed by more detailed prospective studies, are significant because they suggest the possibility of a broad range of new therapies that mimic the systemic effects of renal failure. Thus, the benefits of cytoreductive nephrectomy in metastatic renal cancer demonstrated in the SWOG 8949 and European Organization for Research and Treatment of Cancer (EORTC) studies may, in fact, be applied to a much broader range of metastatic cancers.

Footnotes

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3 The abbreviations used are: IL, interleukin; BUN, blood urea nitrogen; SWOG, Southwest Oncology Group; pH, extracellular pH.

3 E. T. Gawlinski and R. A. Gatenby, unpublished observations.

4 These values do not correspond to those presented in Ref. 10. In this report, we have adjusted the pH threshold for death and quiescence for both tumor and normal cells to be more biologically accurate. Because the death and quiescence thresholds were taken to be lower in Ref. 10 than in this study, a qualitative reduction in tumor growth with decreasing serum pH would still be observed using the former values; however, the degree of acidification required to achieve the same growth-rate reduction reported herein would be larger.

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