Regarding the focal treatment of prostate cancer: Inference of the Gleason grade from MR spectroscopic imaging

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Abstract

Purpose—The question of whether magnetic resonance spectroscopic imaging (MRSI) can be used to predict the Gleason score has been recently examined at our institution (1) and higher Gleason grade was associated with higher R=(choline+creatine)/citrate values. We wish to quantify this correlation by calculating as a function of R the probability that a particular voxel has a pathologic Gleason score ≥4+3, with sextant biopsy BxG and lesion volume V as cofactors.

Methods and Materials—The data consist of MRSI ratios R stratified by patient, lesion (contiguous abnormal voxels), voxels, biopsy and pathologic Gleason, and lesion volume. The data were analyzed using a logistic model.

Results—For both low- and high-Gleason biopsy lesions, the probability of pathologic Gleason score ≥4+3 increases with lesion volume. At low values of *R* a lesion volume of at least 15–20 voxels is needed to reach a probability of success of 80%; the biopsy result helps reduce the prediction uncertainty. At larger MRS ratios (*R*>6) the biopsy result becomes essentially uninformative, once the lesion volume is >12 voxels. With the exception of low values of *R,* for lesions with low-Gleason score at biopsy, the MRS ratios serve primarily as a selection tool for assessing lesion volumes.

Conclusions—In patients with biopsy Gleason score ≥4+3, high MRSI tumor volume and (Cho +Cr)/Cit may justify the initiation of voxel-specific dose escalation. This is an example of biologically-motivated focal treatment for which IMRT and especially brachytherapy are ideally suited.

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Conflict of Interest: none

Keywords

prostate cancer; focal treatment; magnetic resonance spectroscopic imaging; Gleason grade

INTRODUCTION

In this article we defend the claim that MR spectroscopy (MRS) is informative with respect to the Gleason grade of prostate cancer. To do this we make use of a unique set of measurements of these two quantities (MRS metabolic data and Gleason grade) concurrently available on a spatial grid of prostate sub-volumes (1). An initial investigation of theses results has already noted that patients with higher grade Gleason often have a higher ratio of (creatine + choline)/ citrate (1) and here we further advance this analysis with the goal of quantifying, as a function of average MRS score and tumor volume, the probability that a cancer-suspected lesion does indeed have an elevated Gleason grade.

Routine treatment options for the patient with localized prostate cancer (surgery, radiation) share similar outcomes in terms of their capability to suppress PSA-producing tissue (the so-called "biochemical" response) or, more importantly, prevent distant failure and/or cause-specific death. Faced with uncertainty on whether the treatment of local disease will have a benefit in terms of life expectancy, an informed patient will likely select a treatment modality based on its reported ability to minimize ensuing morbidity. This is particularly relevant in the era of serum PSA screening where the typical patient is increasingly younger and some 10 years away from the manifestation of any clinical symptoms, yet under the threat of significant treatment-related sequelae (impotence, urethral incontinence and bowel injury).

The advent of intensity-modulated radiation therapy (IMRT) and intra-operative planning in brachytherapy (BRT) has contributed significantly to reducing some side effects (2–5) (urethral and rectal toxicity) but progress along this direction is likely reaching its limits. The next challenge to overcome in this respect is treating only those lesions in the prostate gland that contain clinically significant (as opposed to indolent) cancer, essentially cells that have the ability to invade and metastasize. The sine qua non of this line of attack – known as *focal treatment* – is the ability to find and localize the corresponding biomarkers (6).

Gleason score is generally acknowledged as predictive of distant failure and its consequences (7) (8). The question of whether magnetic resonance spectroscopic imaging (MRSI) – a non-invasive in vivo technique that maps the metabolic profile of prostate tissue – can be used to predict this quantity has been recently examined at our institution (1). Higher Gleason grade tumors were associated with higher values of the ratio $R = $ (choline + creatine)/citrate. In this follow-up analysis we wish to quantify this correlation by calculating, as a function of R, the probability that a particular lesion, defined as a contiguous assembly of voxels considered suspicious for cancer by MRS analysis, has a certain pathologic Gleason score (G). We include as cofactors in our model the results of sextant biopsy Gleason grading (BxG) and the lesion volume, V. By the conclusion of this analysis we shall have developed a convenient functional probability model for Gleason grade forecasting.

We shall argue that for patients with biopsy Gleason score BxG $\geq$4+3 (representing poorly differentiated tumors) the lesion volume V alone, estimated from the MRSI data, is predictive of similar pathologic score. On the other hand, for patients with BxG<4+3 both the lesion volume V and the MRSI ratio R determine the probability that G$\geq$4+3. Furthermore, if high Gleason sums are correlated with cell proliferation - as some reports suggest (9) - this would appear to justify the initiation of lesion-specific dose escalation. This in effect will be the overall conclusion of our paper.

METHODS AND MATERIALS

Patient Data

The structure of the data set, described in more detail in Zakian et al (1), is explained schematically in Table 1. It consists of a total 142 lesions (a set of voxels that satisfy the constraints set below) comprising a total of 885 voxels. The following information was available for each voxel:

a. The MRSI ratio, R (when larger than 0.5)

b. The volume (number of voxels) of the lesion to which the voxel belongs, V

c. A categorical variable, y, indicating whether at pathologic analysis the Gleason score of the lesion containing this voxel was smaller or larger/equal than 4+3 (y=0 if G<4+3; y=1 if G≥4+3)

d. A categorical variable, Z, specifying – for that particular patient – the result of the sextant biopsy (Z=0 if BxG<4+3; Z=1 if BxG≥4+3)

Only voxels that belonged to true positive (TP) or false negative (FN) lesions confirmed to have cancer (true/false refers to lesions with pathological confirmed/refuted cancer) are included in the analysis. As well, the data are restricted to voxels in the peripheral zone of the prostate. 106 voxels were categorized as false negatives (FN) and consequently the MRSI score (less than 0.5) was not recorded. Among these, the proportion of voxels with G≥4+3 was less than 5%, and they were not included in the analysis. The distribution of lesions by pathologic Gleason score (y=0,1) and biopsy Gleason score (Z=0,1) is shown in Table 2. We characterize each lesion by the *average* value, $\bar{R}$, of its voxels' MRS scores, a procedure consistent with the MRS ratio expected should the lesion had been measured as a single unit. Table 3 shows, as a function of Z and Y, lesion-averaged ratios, $\bar{R}$, and volumes (denoted $<\bar{R}>$ and $<V>$, respectively).

Data Analysis

Let y be a discrete random variable over the set (0,1) that indicates whether a given lesion has pathologic Gleason score, G≥4+3 ($y = 1$) or G<4+3 ($y = 0$). We shall consider y a Bernoulli variable subject to the binomial distribution:

$$\Pr\{y|\pi\} = \pi^y(1-\pi)^{1-y} \tag{1}$$

where the probability of success (i.e. a high grade lesion), π, is taken to depend on a group of three explanatory variables: R (the MRS ratio, R≥0.5), Z (biopsy Gleason score dichotomized in the same manner as y) and V (the volume of the lesion containing the voxel of interest). A commonly utilized analytic expression to describe the relationship between π and R, Z and V is the logistic model. Thus:

$$\pi(x,V,Z) = \frac{\exp\left[(\alpha_z + \beta_z x + \gamma_z V)\right]}{1 + \exp\left[(\alpha_z + \beta_z x + \gamma_z V)\right]} \tag{2}$$

where x=log(R). Equivalently:

$$\text{logit}[\pi(x,V,Z)] = (\alpha_z + \beta_z x + \gamma_z V) \tag{2'}$$

$(x, y, V, Z, \alpha_Z, \beta_Z, \gamma_Z)$ is a random vector and we are concerned with estimating the marginal probability distribution function of the vector $\bar{\phi} = (\alpha_Z, \beta_Z, \gamma_Z)$ from a sample of observed values $D=(x_i, y_i, V_i, Z_i)$, $i=1,\dots n$.

The procedure we propose is the following. Using Bayes theorem (10):

$$p(\bar{\phi}|D) \propto p(\bar{\phi})\,p(D|\bar{\phi}) \tag{3}$$

$$p(\bar{\phi}|D) \propto p(\bar{\phi})\prod_{i=1}^{n}\pi_{\bar{\phi}}(x_i,V_i,Z_i)^{y_i}\left[1-\pi_{\bar{\phi}}(x_i,V_i,Z_i)\right]^{1-y_i} \tag{4}$$

Non-informative (i.e., approximately "flat") priors were assumed for the elements of $p(\phi\rightarrow)$. With this, the probability of success ($y=1$) for a voxel with explanatory variables (R_f, V_f, Z_f) is given by the expectation value (E) of $\pi_{\bar{\phi}}(R_f, V_f, Z_f)$ over $\bar{\phi}$:

$$\Pr(y=1|R_f,V_f,Z_f)=\int_{\Phi}\frac{\exp\left[\left(\alpha_z+\beta_z x_f+\gamma_z V_f\right)\right]}{1+\exp\left[\left(\alpha_z+\beta_z x_f+\gamma_z V_f\right)\right]}p(\bar{\phi}|D)d\bar{\phi} \tag{5}$$

$$=\underset{\bar{\phi}}{E}\left[\pi_{\bar{\phi}}(R_f,V_f,Z_f)\right] \tag{5'}$$

In the next section we apply this formalism to the data on hand.

RESULTS

In what follows we estimate the probability distribution function $p(\bar{\phi}|D)$ and then calculate the expected probability of success for different combinations of MRSI ratio, biopsy results (referred to as low-Gleason biopsy, when $Z=0$ and high-Gleason biopsy when $Z=1$) and lesion volumes – all observable quantities. Mathematica 6.0 (11) was used for all calculations. The logistic parameters, Eqs(2,2'), are given in Table 4.

In examining the results one should keep in mind that what we consider here is ultimately a clinical decision problem, namely whether for a particular lesion in the gland, the probability that G≥4+3 is large enough, say at least 80%, to justify a way of clinical action – for instance further dose escalation on top of the standard treatment.

Figs.1 and 3 show, respectively, $\Pr(y=1|Z=0)$ and $\Pr(y=1|Z=1)$ as a function of R and V, revealing the significance of the MRS ratio for the $Z=0$ cohort, and the dominant influence of volume for both cohorts. Representative 95% probability intervals for, respectively, $\Pr(y=1|Z=0)$ and $\Pr(y=1|Z=1)$ are shown in Figs.2 and 4. The ability to quantify the uncertainty associated with an estimate of $\Pr(y=1)$ is a key element of the current method's support for the aforementioned clinical decision problem. Figs.5–9 explore the relationship between Z, V, R and $\Pr(y=1)$ by comparing point estimates of $\Pr(y=1)$, and the associated 95% probability bands, for the same MRS ratios and volumes across the $Z=0$ and $Z=1$ cohorts. With the exception of "low" R and V values in figure 5, sextant biopsy has little effect on either the point estimates or uncertainty.

The results of this analysis, tempered by the informational content of the data, are consistent with the view that:

a. For lesions with both low- ($Z=0$, Fig. 1) and high-Gleason biopsy score ($Z=1$, Fig. 3), $\Pr(y=1)$ increases notably with lesion volume,

b. At low values of R a lesion volume of at least 15–20 voxels is needed to reach a probability of success of 80% (Fig. 5); the biopsy result (Z) helps reduce the uncertainty of the predicted probability of success.

c. At larger MRS ratios ($R>6$, Figs.6–9) the biopsy result becomes essentially uninformative, once the lesion volume is larger than about 12 voxels

d. With the exception of low values of R at $Z=0$, the MRS metabolite ratios serve primarily as a selection tool for assessing lesion volumes.

CONCLUSIONS

The probability distributions asserted here display the information we hold on this matter. We have identified three factors, all potentially available at the time of treatment planning, which can be used to evaluate the probability that a lesion has (pathologic) Gleason grade $\geq 4+3$: biopsy Gleason grade, lesion volume and the average lesion MRS ratio. The presentation here has been oriented to highlight an understanding of this probability with the goal of deciding whether a particular lesion should be treated differently, e.g. with a larger than the customary dose.

In outline, the data and probabilistic model are supportive of the notion that large lesion volumes (e.g. >25) will contain, with high probability, high Gleason voxels irrespective of the biopsy result and/or MRSI ratio. The biopsy result appears mildly relevant at intermediate lesion volumes, and so is the MRSI ratio, R, for lesions with low biopsy Gleason.

The two main limitations of the data available for this study have to do with inadequate spatial resolution: a) the unavailability of pathologic Gleason grade at voxel (rather than lesion) level, and b) the lack of Gleason information for each biopsy core. The latter can be readily dealt with. To identify the MRS prostate voxel in a pathology specimen is a difficult problem; but the necessary methodology – essentially, the mechanics of deformable bodies – exists and has been in fact used already for prostate volumes (12).

The practical import of these findings derives from the possibility of conducting focal treatments and thus avoiding, or at least lessening, patient injury. One must recognize, however, that at this time we remain ignorant of whether there are radiosensitivity and/or proliferative differences between indolent (low Gleason) and aggressive (high Gleason) lesions (i.e. do we need dose escalation?), and – at a more basic level – whether inactivating such lesions prevents distant failure (i.e. why bother?). Answers to these questions are, however, beyond the scope of this analysis.

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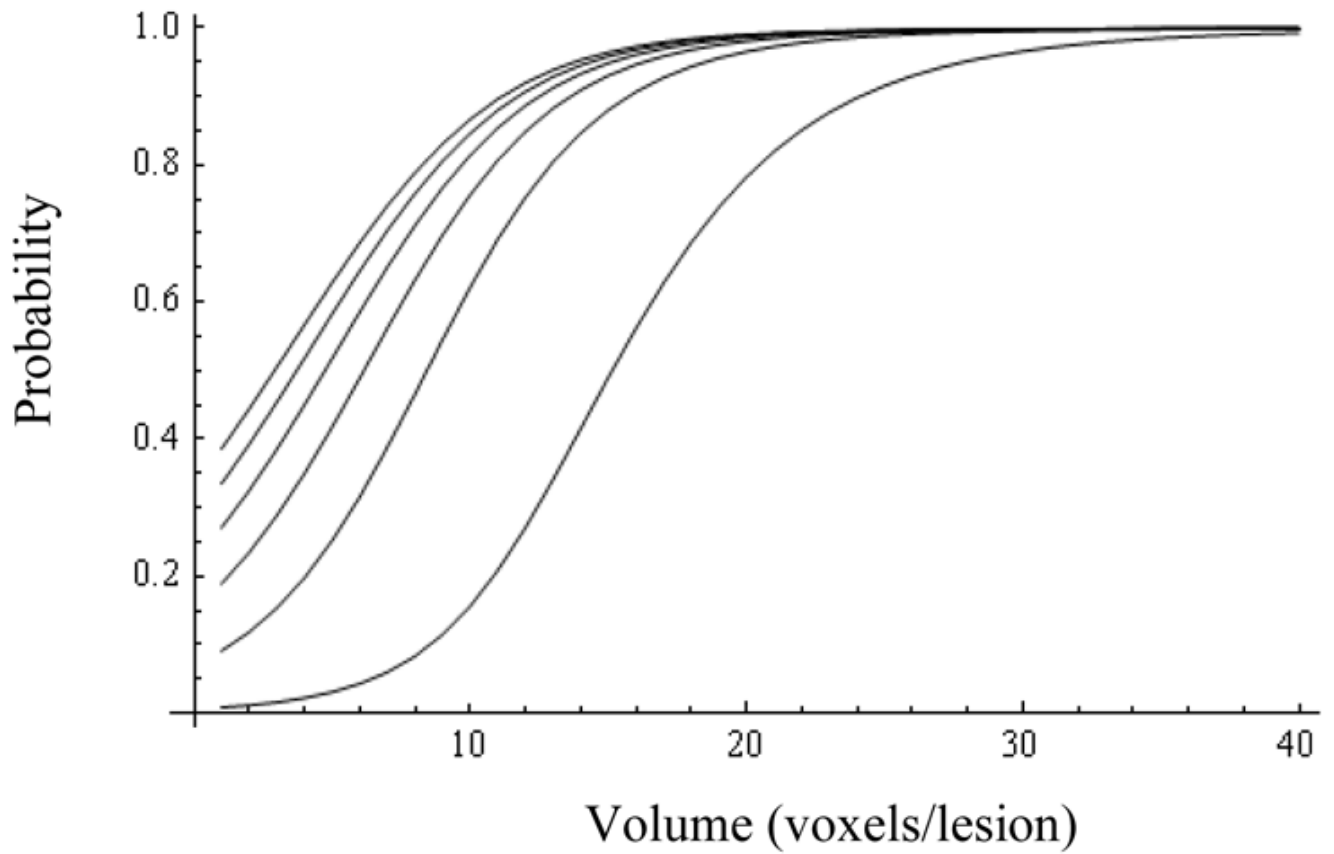
Fig. 1.
Probability of success (y=1) for patients with negative biopsy (Z=0) as a function of volume (abscissa) and MRS ratio (from bottom up: *R*=1, 6, 11, 16, 21, and 26).
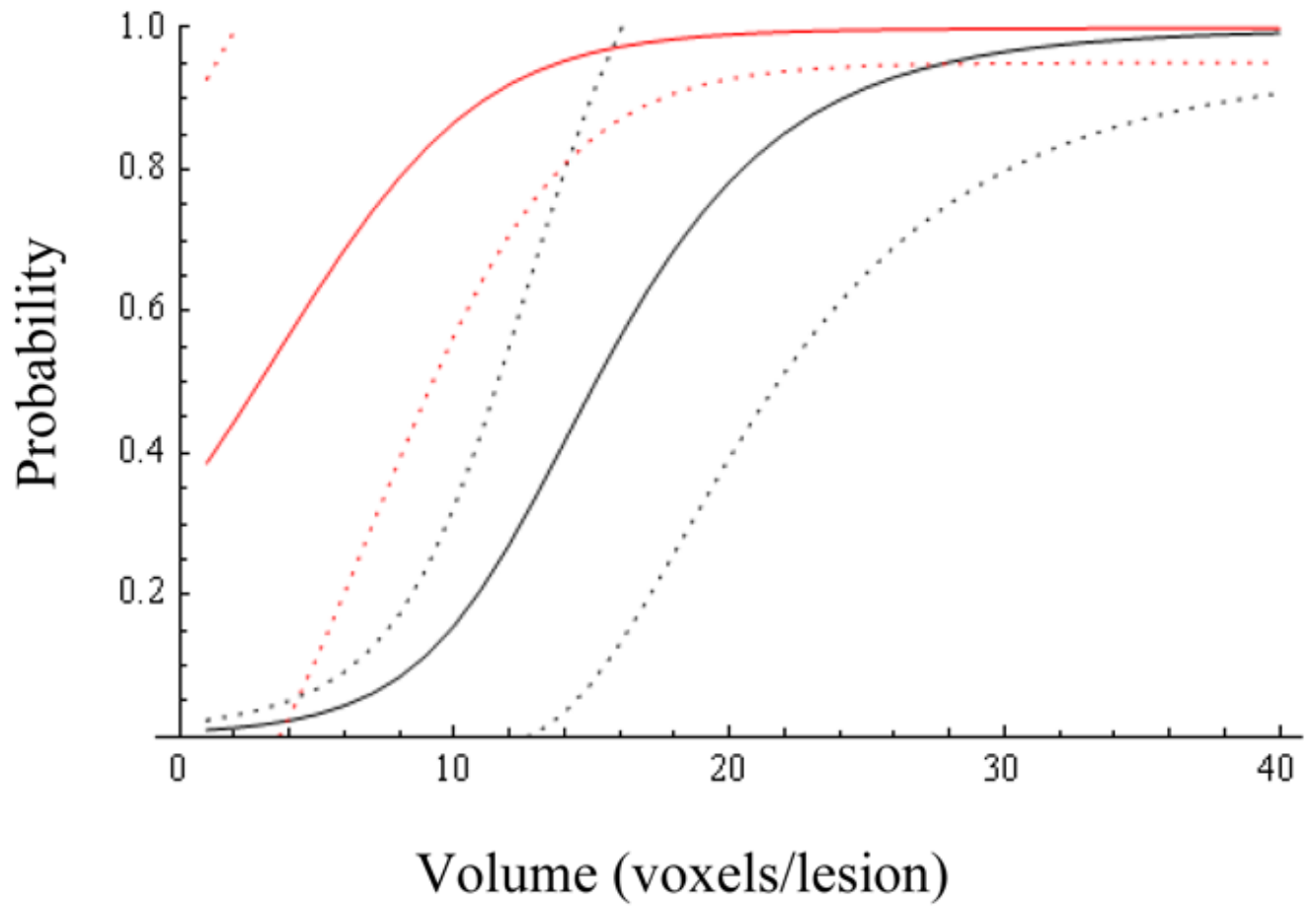
Fig. 2.
Probability of success and 95% confidence bands for patients with negative biopsy as a function
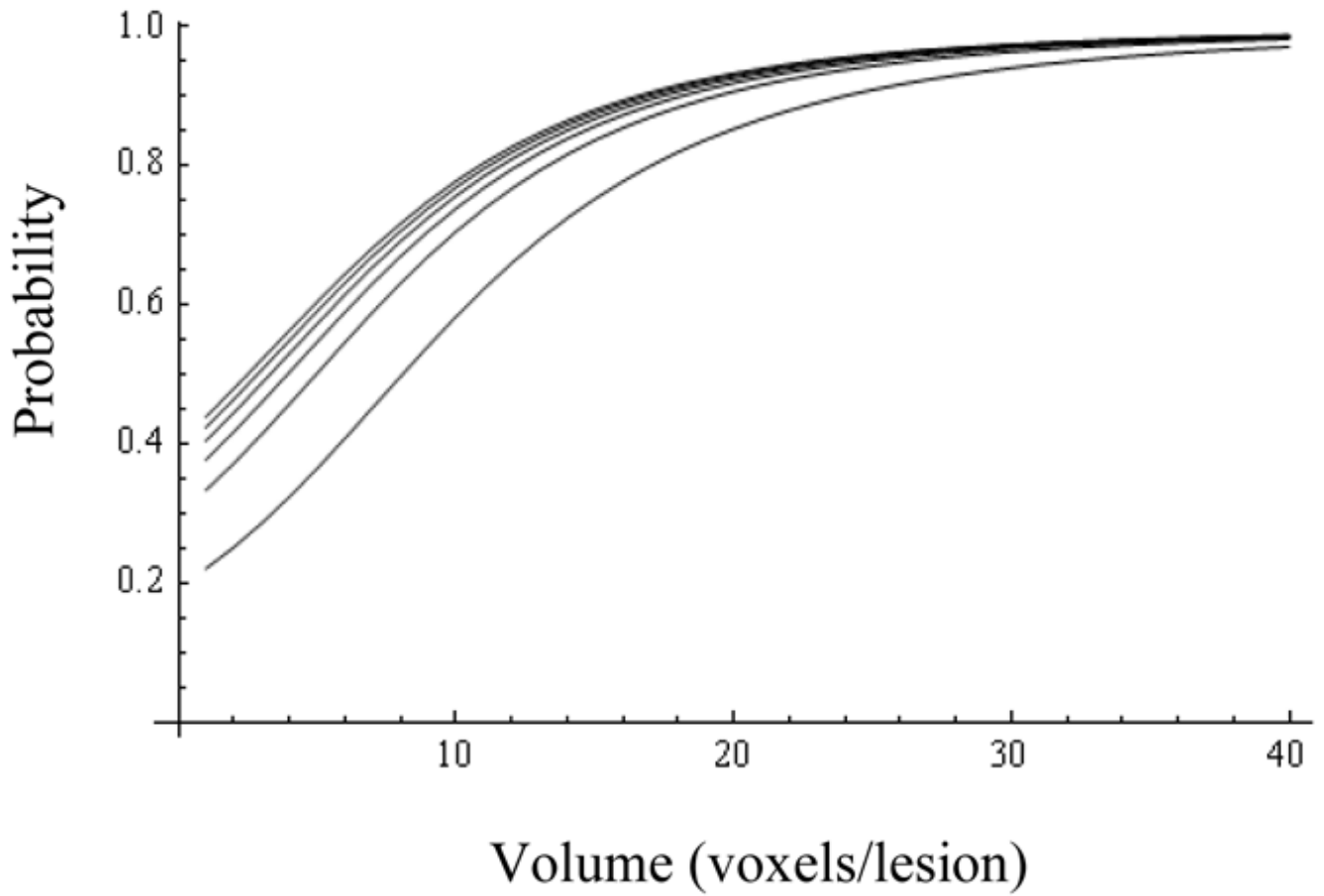of volume (abscissa) and MRS ratio (1=black, 26=red).

Fig. 3.
Probability of success for patients with high biopsy Gleason (Z=1) as a function of volume (abscissa) and MRS ratio (from bottom up: 1, 6, 11, 16, 21, and 26).
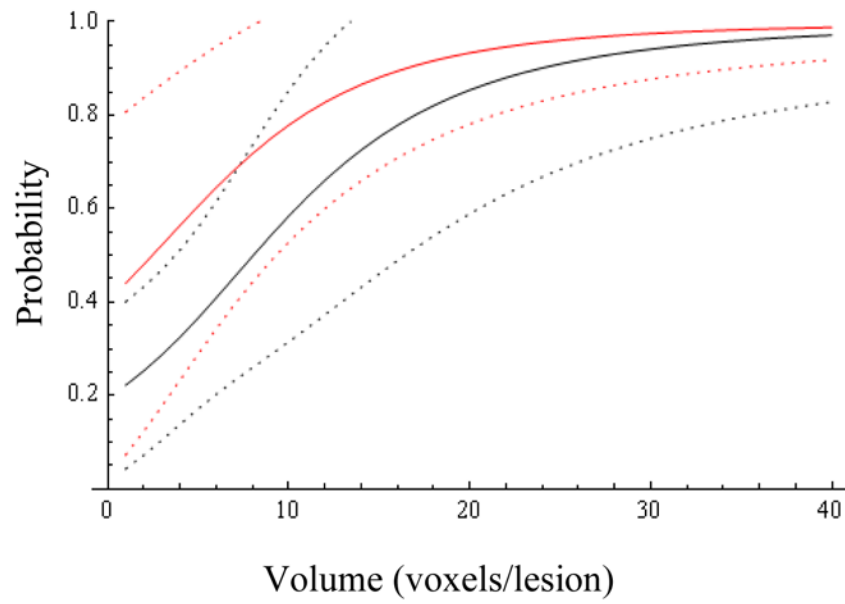
Fig. 4.
Probability of success and 95% confidence bands for patients with high biopsy Gleason (Z=1) as a function of volume (abscissa) and MRS ratio (1=black, 26=red).
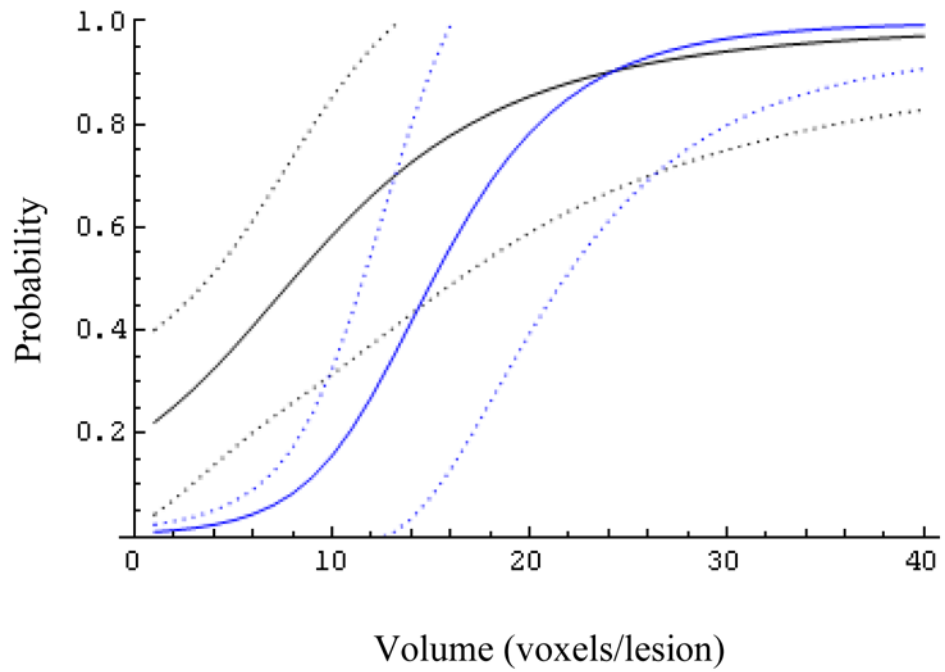
Fig. 5.
The effect of the biopsy result (Z=0 blue, Z=1 black) on the expected probability of success and its 95% confidence bands for patients with MRS ratio 1.

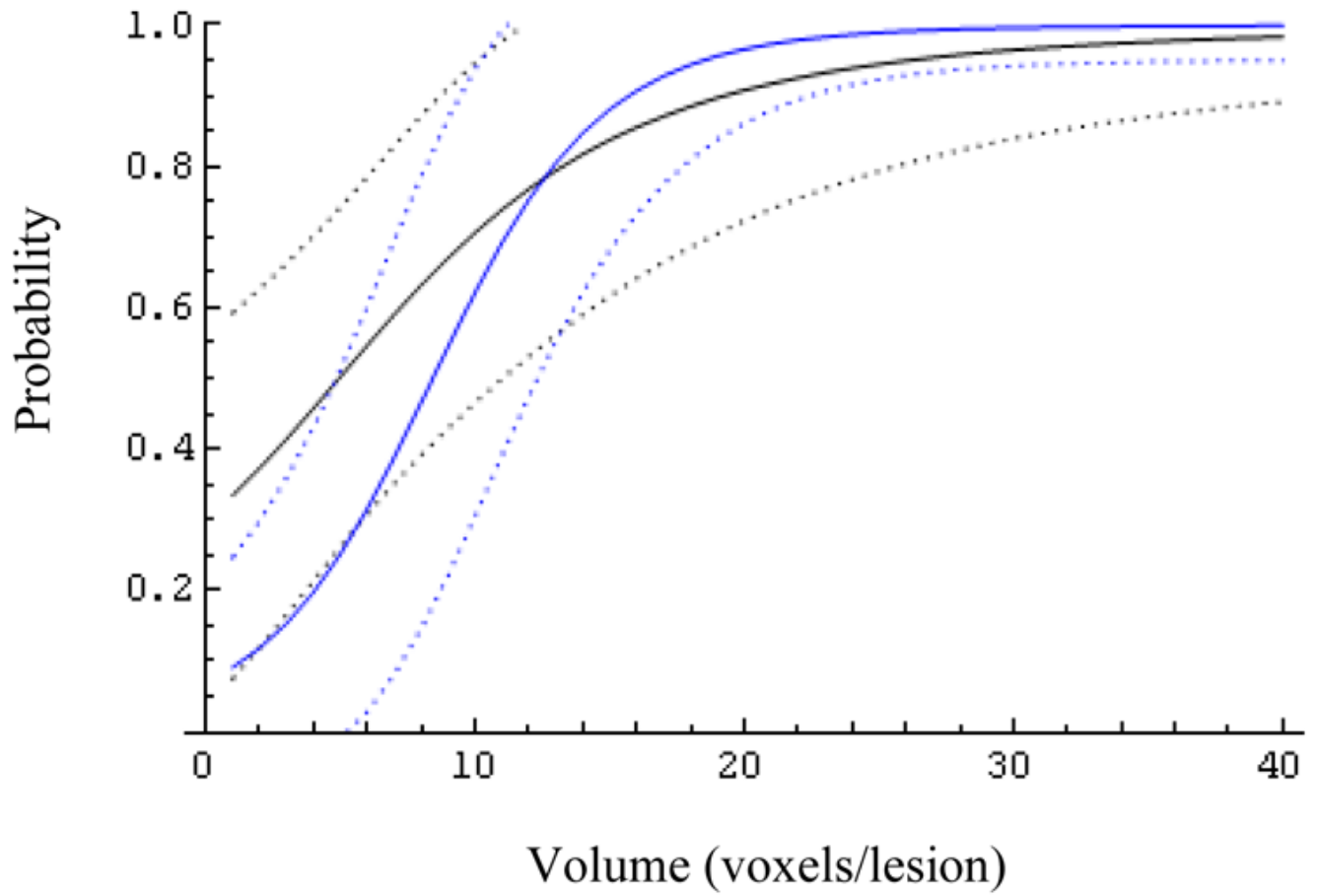**Fig. 6.**
The effect of the biopsy result (Z=0 blue, Z=1 black) on the expected probability of success
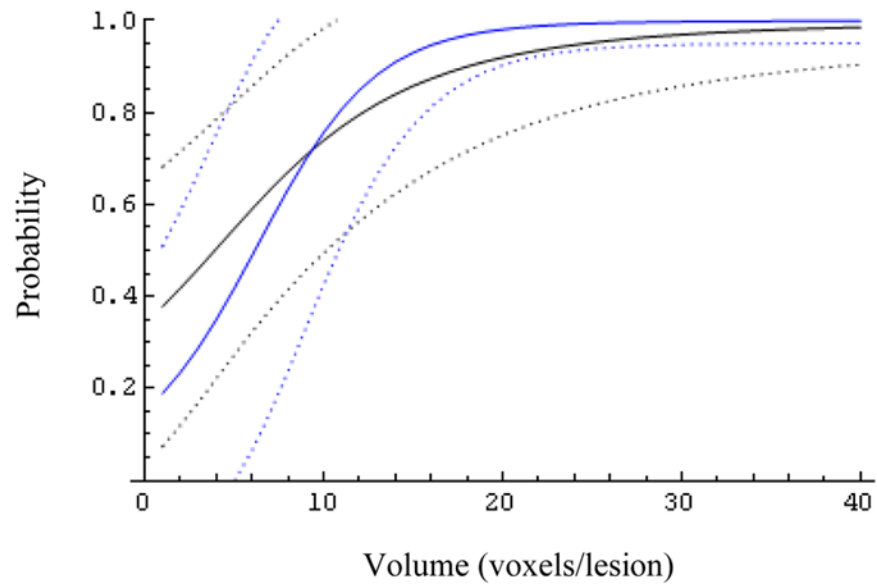and its 95% confidence bands for patients with MRS ratio 6.

Fig. 7.
The effect of the biopsy result (Z=0 blue, Z=1 black) on the expected probability of success and its 95% confidence bands for patients with MRS ratio 11.

Fig. 8.
The effect of the biopsy result (Z=0 blue, Z=1 black) on the expected probability of success and its 95% confidence bands for patients with MRS ratio 21.

Fig. 9.
The effect of the biopsy result (Z=0 blue, Z=1 black) on the expected probability of success and its 95% confidence bands for patients with MRS ratio 26.

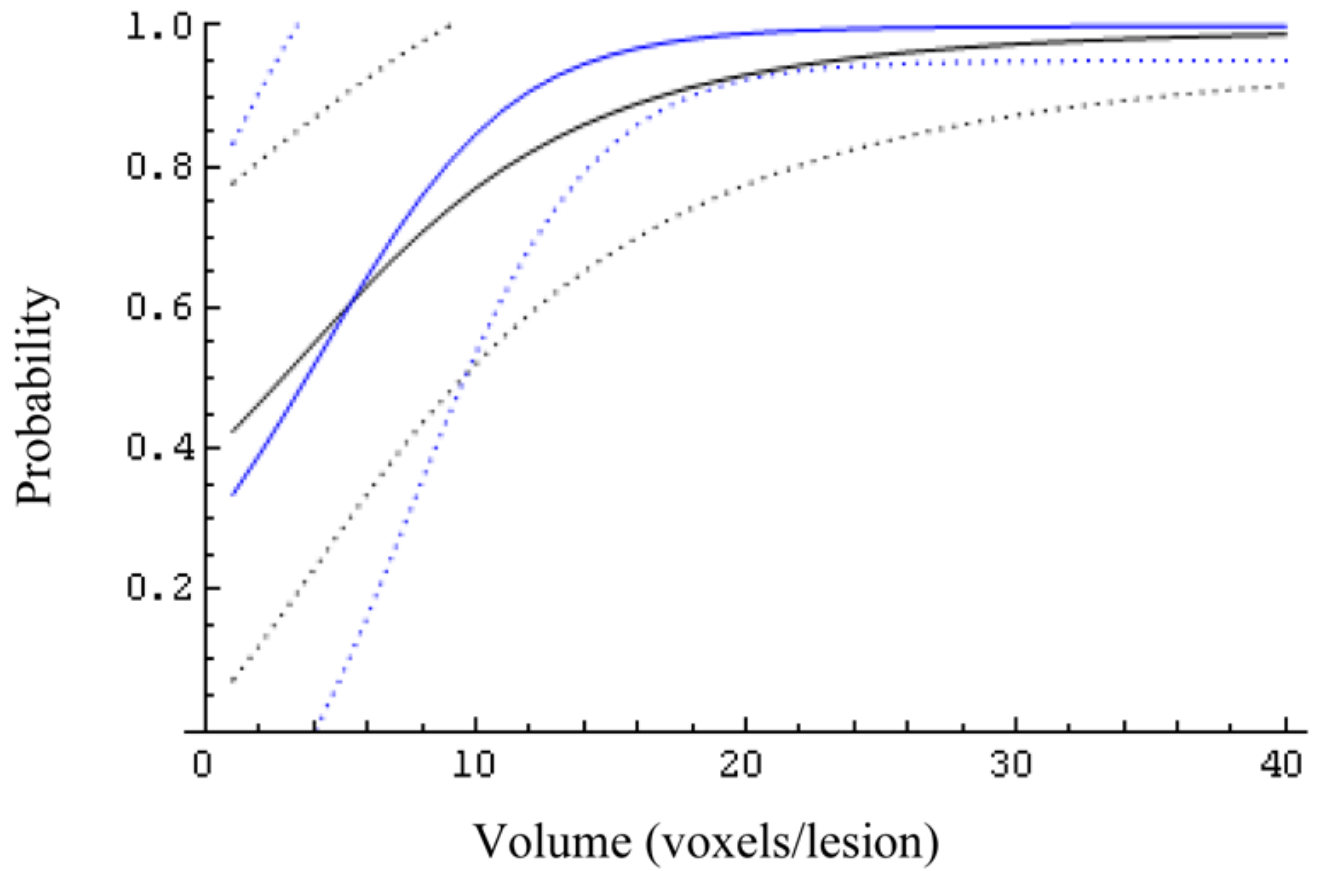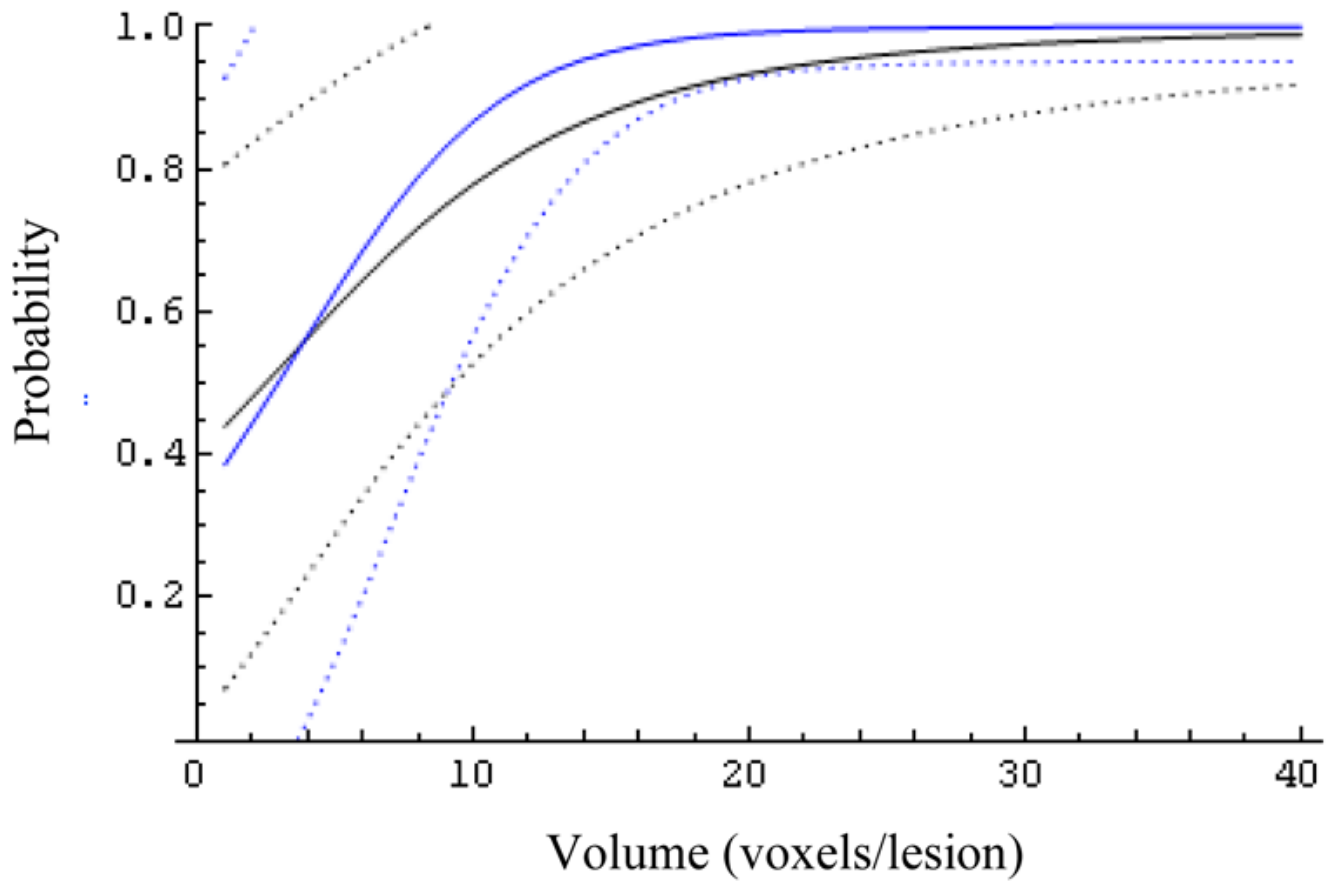**Table 1**

Schematic representation of the structure of the data set used in this analysis. The total number of patients was 88. ($y=0$ if G<4+3; $y=1$ if G$\geq$4+3)

Patient #	Biopsy Gleason (0/1)	Lesion #	Pathologic Gleason, y (0/1)	Voxel #	R	R	V
1	0	1	0	1	0.7		
				2	0.9	0.93	3
				3	1.2		
		2	1	1	2.3	1.55	2
				2	0.8		
		3	0	1	6.7		
				2	1.1	2.70	4
				3	2.1		
				4	0.9		

Table 2

Distribution of lesions by biopsy and pathology Gleason. (*Z*=0 if BxG<4+3; *Z*=1 if BxG≥4+3)

Z (BxG)	Number of Lesions	Pathology Gleason	
		y=1	*y*=0
0	161	13	148
1	33	15	18

Table 3

Lesion-averaged MRS ratios and volumes

Z (BxG)	y=0	y=1
0	$\langle \bar{R} \rangle$=1.1 $\langle V \rangle$=2.9	$\langle \bar{R} \rangle$=3.7 $\langle V \rangle$=17.7
1	$\langle \bar{R} \rangle$=3.8 $\langle V \rangle$=3.8	$\langle \bar{R} \rangle$=3.4 $\langle V \rangle$=10.6

Table 4

Logistic parameters (± 1 SD) for low-Gleason (subscript 0) and high-Gleason (subscript 1) dichotomized biopsy Gleason score (Z in the text)

α_0	β_0	γ_0	α_1	β_1	γ_1
-5.4 ± 0.96	1.33 ± 0.55	0.36 ± 0.10	-1.53 ± 0.61	0.33 ± 0.24	0.19 ± 0.08