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HYPOXIC REGIONS EXIST IN HUMAN PROSTATE CARCINOMA

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ABSTRACT

Objectives. The purpose of this study was to characterize, by use of the Eppendorf microelectrode, the extent of hypoxia (range/heterogeneity) in human prostate carcinomas.

Methods. Custom-made Eppendorf pO_2 microelectrodes were used to obtain pO_2 measurements from the pathologically involved side of the prostate, as well as from a region of normal muscle for comparison. Each set of measurements comprised approximately 100 separate readings of pO_2, for a total of 2145 individual measurements. Twelve patients were studied, 7 of whom underwent brachytherapy, 3 a radical prostatectomy, and 2 a cystoprostatectomy. The pO_2 measurements were obtained in the operating room, using sterile technique, under spinal anesthesia for the brachytherapy group patients and under general anesthesia for the surgery group patients. The Eppendorf histograms were recorded and described by the median pO_2, mean pO_2, and percentage of measurements less than 5 mm Hg and less than 10 mm Hg.

Results. Because of differences in patient characteristics and the anesthesia employed, control measurements were obtained from nearby normal muscle as an internal control in all but 2 patients. This internal comparison showed that the oxygen measurements from the pathologically involved portion of the prostate were significantly lower than those from normal muscle. Similarly, higher pO_2 readings were obtained from the pathologically normal prostates (in the patients with bladder cancer) than from the prostates of patients with prostate carcinoma. Increasing levels of hypoxia were observed with increasing clinical stage. Significant predictors of oxygenation include the type of tissue (pathologically involved prostate versus normal muscle or normal prostate), clinical stage, and type of anesthesia.

Conclusions. This report, to our knowledge, represents the first study to obtain in vivo electrode measurements of oxygen levels in patients with prostate cancer and suggests that hypoxic regions exist in human prostate carcinoma. More patients will be accrued to this prospective study to correlate the oxygenation status of prostate carcinoma with known prognostic factors and treatment outcome. UROLOGY **53:** 11–18, 1999.

The most important predictors of outcome in prostate cancer known to date are pretreatment prostate-specific antigen (PSA) level, Gleason score, and clinical stage. We previously demonstrated that a variety of models in published reports incorporating these prognostic factors are essentially equivalent in predicting outcome.[1] Despite these factors, it is difficult to predict treatment failure in individual patients. We hypothesized that an underlying biologic variable, the oxygenation status of the prostate cancer, is a key predictor of outcome that may refine the above models. Several studies have shown a significant relation between the extent of hypoxia and treatment outcome of other tumors after radiotherapy.[2–5] One study demonstrated that hypoxic regions in tumors even predicted poor tumor response after surgery, suggesting that hypoxia may promote tumor aggressiveness and metastases.[6] Several preliminary clinical[7–9] and animal studies[10,11] suggest the presence of hypoxic cells in some prostate carcinomas. To date, however, no such in vivo measurements have been reported for prostate carcinoma. The Eppendorf pO_2 microelectrode histograph has greatly enhanced our ability to perform multiple pO_2 measurements within human cancers. The purpose of the current

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study was to characterize, by use of the Eppendorf microelectrode, the extent of hypoxia (range/heterogeneity) in human prostate carcinoma.

MATERIAL AND METHODS

In this study, pO_2 measurements were taken from the pathologically involved side of the prostate as well as a region of normal muscle for comparison. Patients were treated either by surgery (radical prostatectomy) or by radioactive implantation of the prostate. The pO_2 measurements were obtained in the operating room, through sterile technique, and under anesthesia (spinal anesthesia with tetracaine for the brachytherapy group patients and fluorine-based general anesthesia for the surgery group patients). Eligible patients for this study were those with histologically confirmed prostate adenocarcinoma, American Joint Committee on Cancer (AJCC) Stage T1C to T3C, with no clinical or pathologically involved lymph nodes and no evidence of distant metastases. The patients had a Karnofsky performance status of 70 or higher and had not received prior chemotherapy, hormonal therapy, or pelvic radiotherapy. Pretreatment PSA measurement was mandatory, as was pathologic review of the specimen at Fox Chase Cancer Center. To determine the oxygenation status of normal prostatic tissue, measurements were also obtained from 2 patients undergoing cystoprostatectomy for bladder cancer. All patients signed an institutional review board-approved study-specific consent form.

To reach the prostate through the perineal template used for brachytherapy, custom-made 12 to 14-cm microelectrodes were manufactured and obtained from Eppendorf (Hamburg, Germany). The electrode measurements were performed before the brachytherapy procedure to avoid potential measurement artifacts secondary to vascular disruption. Initially, pO_2 measurements were obtained from a region of periprostatic muscle as a control. Measurements were then obtained from the pathologically involved portion of the prostate, as determined from sextant biopsy information. Real-time ultrasound imaging was used to precisely place a trocar through the perineal template in the region of interest in the prostate. The Eppendorf microelectrode was carefully passed through this trocar, and measurements were taken (beyond the distal edge of the trocar) in the proper location within prostatic tissue. To ensure that the use of the trocar itself was not leading to spurious results, this technique was tested in the laboratory with Dunning prostatic tumors growing in rats. The median value of the Eppendorf pO_2 measurements without the trocar was not significantly different from that taken through the trocar (15.2 and 19.9 mm Hg, respectively).

In the surgical group patients, the pO_2 measurements were obtained under direct visualization, obviating the need for measurements through a trocar. After the nodal dissection and before vascular disruption of the prostate, measurements were initially taken from the psoas muscle as a control. Measurements were then obtained, through an anterior approach, from the pathologically involved side of the prostate, as determined by the pretreatment sextant biopsies. This was facilitated by incising the endopelvic fascia without dividing the dorsal vein complex or the prostatic pedicles. If a region of nodularity was present, measurements were taken directly from that area. The findings were correlated with the final pathologic review.

In both the surgery and brachytherapy group patients, each set of measurements (in both the prostate and control tissue) comprised approximately 100 separate readings of pO_2 that were obtained along three to four separate electrode tracks.[10] This procedure (including the prostate and control measurements) took approximately 10 to 15 minutes. Control readings were not obtained in the first 2 surgical group patients (performed on the same day) because of timing considerations in these initial cases. Immediately after the measurements, patients went on to undergo prostatectomy or brachytherapy implantation.

For the measurement of tissue pO_2, a gas-sterilized 12 to 14-cm polarographic needle electrode with a stainless steel shaft was used (pO_2 Histograph, model 6650, Eppendorf). The probes have a mean shaft diameter of 0.3 mm. Calibration was performed in a sterile phosphate-buffered saline solution (pH 7.8 to 8.4) immediately before and after each set of pO_2 measurements in tissue. The electrode was automatically moved through the tissue in precise steps of 0.7 mm. Each rapid forward step was immediately followed by a backward step of 0.3 mm to minimize compression effects caused by the forward motion of the oxygen-sensitive needle electrode. The average oxygen concentration in the extracellular fluid in this tissue volume of approximately 1000 cells was measured in less than 40 ms. The Eppendorf histograms were recorded, as well as the median pO_2, mean pO_2, and percentage of measurements less than 5 mm Hg and less than 10 mm Hg.

Statistical Analysis

Within each patient, comparisons were made of the cumulative distributions of pO_2 measures between tissue groups using the nonparametric Wilcoxon test. Similar comparisons were made parametrically using the Student *t* test. Differences in percentages of measurements less than 10 mm Hg and less than 5 mm Hg were evaluated using the Pearson chi-square statistic. The patients with prostate cancer were combined with those with bladder cancer, and pO_2 measures were modeled as a function of the following factors: tissue, type of cancer, and the interaction thereof. The patients with prostate cancer were pooled, and linear mixed models were used to multivariately assess predictors of pO_2 levels, including stage (T1C versus T2A/T2B), pretreatment PSA levels (less than 5.5 ng/mL versus 5.5 ng/mL or higher), age (younger than 59 years old versus 59 or older), prostate volume (less than 43 cm^3 versus 43 cm^3 or greater), anesthesia (spinal versus general), and tissue type (prostatic versus muscle). Because all but 1 patient had a Gleason score of 6, this covariate could not be analyzed. Separate models were run for stage, anesthesia, tissue type, and their corresponding two-factor interactions; pretreatment PSA levels, anesthesia, tissue type, and their corresponding two-factor interactions; and age, anesthesia, tissue type, and their corresponding two-factor interactions. Mixed-effects modeling is appropriate for repeated measures analyses when variation between and within patients must be accounted for.

RESULTS

Table I shows the age, clinical stage, Gleason score, pretreatment PSA, type of treatment, type of anesthesia, site of the Eppendorf measurement, number of measurements, mean pO_2, median pO_2, and percentage of measurements less than 5 mm Hg and less than 10 mm Hg for each patient studied. Overall, a total of 2145 separate pO_2 readings were obtained from muscle and prostatic tissue in 12 patients, 7 of whom underwent brachytherapy (5 by a ^{125}I permanent low dose rate implant and 2 by a ^{192}Ir high dose rate implant), 3 a radical retropubic prostatectomy, and 2 a cystoprostatectomy for invasive bladder cancer. The mean and median ages were 59 years. Clinical Stage

TABLE I. *Patient characteristics and results*

Pt No.	Age (yr)	Stage	Gleason Score	PSA (ng/mL)	Type of Treatment	Type of Anesthesia	Site of Measurement	No. of Measurements	Mean pO_2 (mm Hg)	Median pO_2 (mm Hg)	<5 mm Hg (%)	<10 mm Hg (%)	*P* Value*
1	66	T1CN0M0	6	8.7	LDR ^{125}I	Spinal	Prostate—right side	77	8.5	5.5	48	68	
							Periprostatic muscle	94	23.2	22.6	3	15	<0.0001
2	68	T1CN0M0	6	9.2	LDR ^{125}I	Spinal	Prostate—left side	85	17.9	13.1	28	44	
							Periprostatic muscle	92	27.9	29.1	9	21	<0.0001
3	53	T1CN0M0	6	4	Radical prostatectomy	General	Prostate—left side	129	40	38.2	6	10	N/A
4	68	T1CN0M0	6	5.5	Radical prostatectomy	General	Prostate—right side	112	32.5	18.6	34	41	N/A
5	44	T2AN0M0	6	4.1	Radical prostatectomy	General	Prostatic nodule—right side	100	9.5	6.1	38	70	
							Psoas muscle	98	28.4	26.5	0	2	<0.0001
6	70	T2AN0M0	6	6.2	LDR ^{125}I	Spinal	Prostate—right side	105	3.2	1.8	88	92	
							Periprostatic muscle	101	20.5	15.6	5	21	<0.0001
7	49	T2AN0M0	6	0.5	LDR ^{125}I	Spinal	Prostate—left side	101	5.7	2.3	84	88	
							Periprostatic muscle	104	27.3	30.1	9.6	11.5	<0.0001
8	50	T2AN0M0	6	3.0	LDR ^{125}I	Spinal	Prostate—right side	112	22.4	20.5	27	35	
							Periprostatic muscle	69	27.5	24.9	1.4	7	0.02
9	59	T2BN0M0	7	7.9	HDR ^{192}Ir	Spinal	Prostate—left side	81	11.8	7.4	36	57	
							Periprostatic muscle	96	29.6	30	0	0	<0.0001
10	64	T2BN0M0	6	21.8	HDR ^{192}Ir	Spinal	Prostate—right side	80	5.4	1.8	65	75	
							Periprostatic muscle	94	29.8	30.9	1	9	<0.0001
11	54	Bladder cancer	N/A	N/A	Radical cystoprostatectomy	General	Prostate—left side	101	31.1	31.3	4	18	
							Psoas muscle	98	10.8	7.6	29	59	<0.0001
12	68	Bladder cancer	N/A	N/A	Radical cystoprostatectomy	General	Prostate—left side	111	20.2	21.0	14	25	
							Psoas muscle	105	10.8	8.0	22	59	<0.0001

Key: Pt = patient; LDR ^{125}I = low-dose-rate ^{125}I permanent implant; N/A = not applicable; HDR ^{192}Ir = high-dose-rate ^{192}Ir implant.
** Nonparametric and parametric* P *values were identical for distributional comparison.*

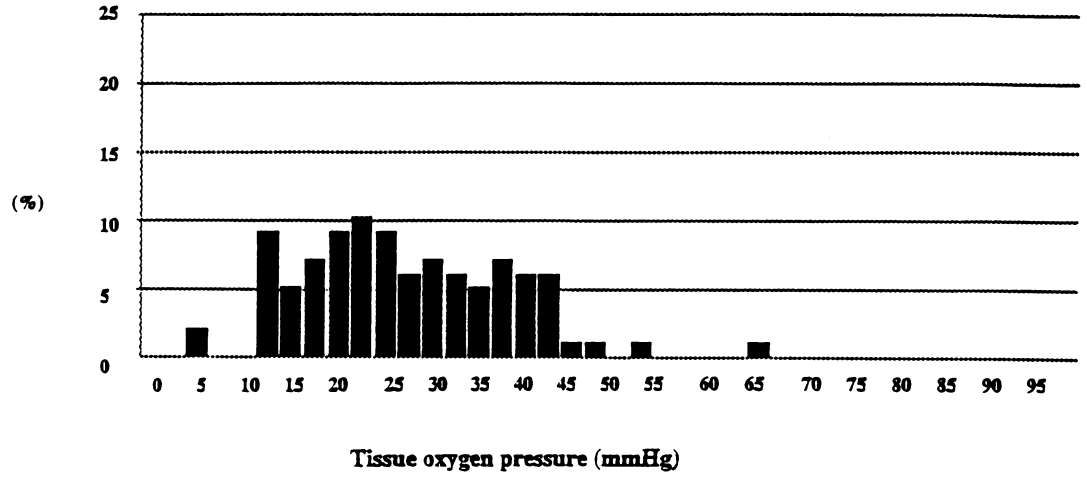

FIGURE 1. *Histogram of pO_2 measurements from normal muscle.*

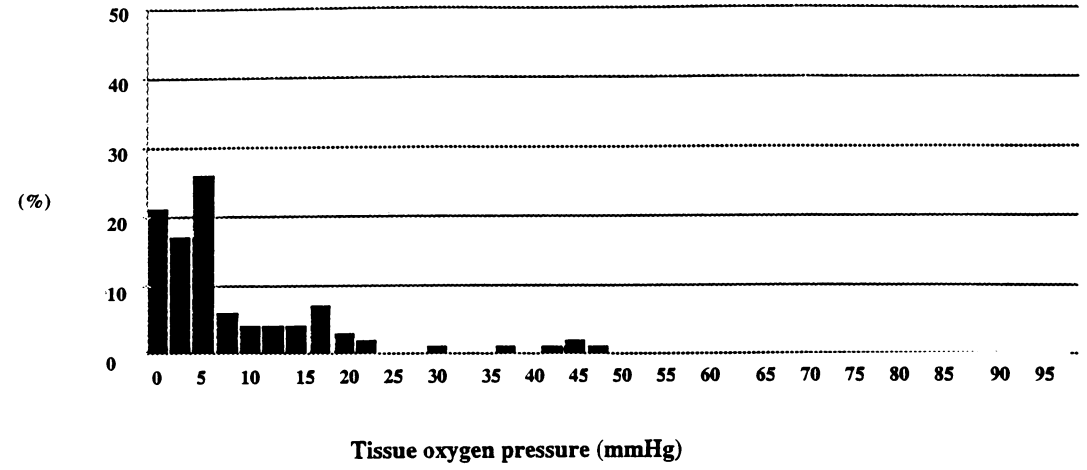

FIGURE 2. *Histogram of pO_2 measurements from prostate cancer nodule.*

T1CN0M0 prostate adenocarcinoma was present in 4 patients, Stage T2AN0M0 in 4, and Stage T2BN0M0 in 2; invasive transitional cell carcinoma of the bladder was present in 2 "control" patients. All but 1 patient (with Gleason score 7) had a Gleason score of 6. The mean and median pretreatment PSA levels were 7.1 and 5.5 ng/mL, respectively. The mean and median prostate volumes (by ultrasound) were both 43 cm^3 (range 30 to 64).

Because each patient (except for 2) had an "internal control" representing normal muscle tissue, comparisons were made for each patient between the measurements from the prostate and measurements from the control muscle tissue. The *P* values for these comparisons (between either the median or the mean values, as well as the percentage less than 10 mm Hg) were all statistically significant. Similarly the *P* values for the percentage less than 5 mm Hg were significant ($P < 0.001$, except for Patient 12). The histograms of pO_2 measurements from muscle and prostate in Patient 5 are shown in Figures 1 and 2, respectively. Patient 5 was the only patient undergoing surgery with a prostatic nodule that could easily be palpated. Figure 1 shows the histogram comprising 98 pO_2 measurements from the psoas muscle (as a control). The mean and median values are 28.4 and 26.5 mm Hg, respectively, with only 2% of the measurements less than 10 mm Hg. By contrast, Figure 2 comprises 100 measurements taken from the region of the palpable nodule (pathologically verified to be prostate adenocarcinoma). In this case, the mean and median values were 9.5 and 6.1 mm Hg, respectively, with 70% of the measurements less than 10 mm Hg. These differences in pO_2 measurements between the prostatic nodule and the normal muscle were all highly significant ($P < 0.0001$).

The pO_2 measurements obtained from the two "normal" prostates demonstrated median pO_2 levels of 31 and 21 mm Hg, with only 18% and 25% of the readings less than 10 mm Hg, respectively. The final pathologic results showed no evidence of car-

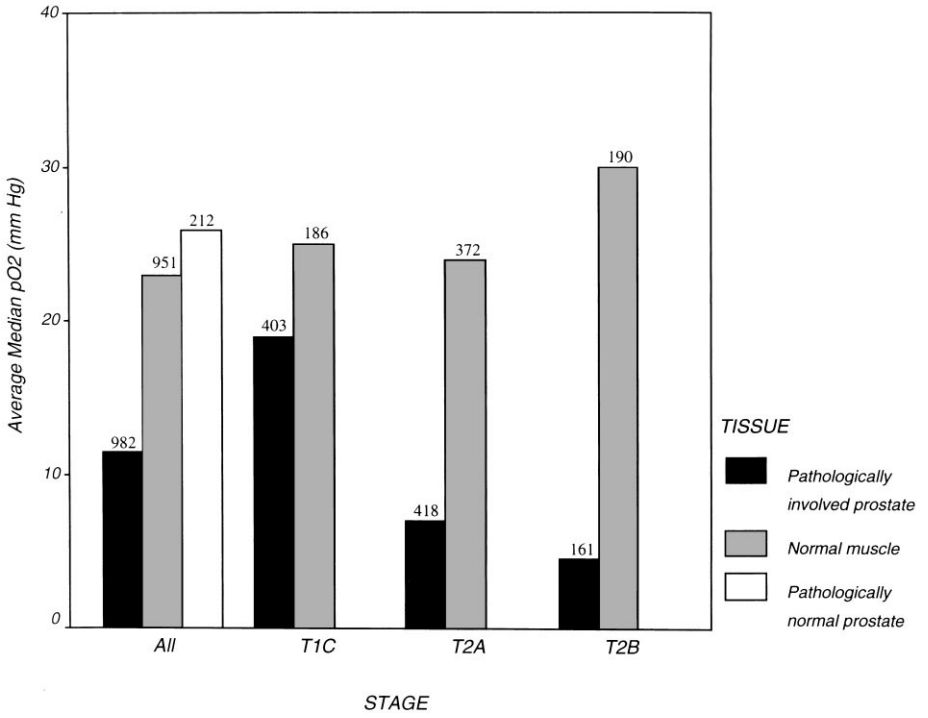

FIGURE 3. *Tissue oxygenation versus clinical stage. Numbers above the bars indicate the number of separate pO_2 measurements taken in that group of patients.*

cinoma within the prostate of these 2 patients who underwent a radical cystoprostatectomy for muscle invasive transitional cell carcinoma of the bladder. Of note, the relatively low pO_2 readings from the psoas muscle in these 2 patients (median pO_2 7.6 and 8.0 mm Hg, respectively, with 59% less than 10 mm Hg) remain an enigma but may be related to different positioning of these patients (possibly causing muscle compression) or differential effects of fluorine-based anesthesia on the different organ vasculatures. The final pathologic results of the 3 patients undergoing radical retropubic prostatectomy for prostate cancer were as follows: all 3 patients had negative pelvic lymph nodes, and all had a Gleason score of 6 for prostate adenocarcinoma, with negative margins and negative seminal vesicles. Patient 3 had involvement of the right posterior, left middle, and posterior lobes but no evidence of perineural invasion. Patient 4 had evidence of cancer in all four quadrants of the prostate, with tumor focally penetrating into but not through the capsule, with evidence of perineural invasion. Patient 5 had cancer involving both lobes of the prostate, confined to the capsule, with evidence of perineural invasion.

The average of the median pO_2 values from all the control muscle measurements was 23 mm Hg compared with the average of the median pO_2 measurements of 12 mm Hg from the pathologically involved prostate and 26 mm Hg from the pathologically normal prostate (Fig. 3). Whereas an increasing level of hypoxia was observed with increasing clinical stage from measurements in the pathologically involved prostate, the pO_2 measurements of the normal muscle remained constant. The mixed-effects modeling of all 12 patients demonstrated that the significant predictor of oxygenation was the interaction between tissue (prostatic versus muscle) and type of cancer (prostate versus bladder, $P = 0.0001$). Significant two-level interaction effects imply that the two factors are jointly predictive of pO_2 value. The mixed effects modeling of the 10 patients with prostate cancer demonstrated that the significant predictors of oxygenation included the type of tissue (prostatic versus muscle, $P \leq 0.0001$), clinical stage ($P = 0.001$), type of anesthesia (general versus spinal, $P = 0.002$), and the interactions between tissue and stage ($P = 0.013$), as well as anesthesia and stage ($P = 0.002$). When controlling for the type of tissue, the significant predictors of the pO_2 measurements in the pathologically involved prostatic tissue included stage ($P = 0.004$), type of anesthesia ($P = 0.03$), and the interaction between anesthesia and stage ($P = 0.03$). For the muscle tissue (control), there were no significant predictors of the pO_2 measurements.

COMMENT

The ability to perform multiple pO_2 measurements within human cancers was greatly facilitated

by the development of the Eppendorf pO_2 microelectrode histograph. This instrument has been used to measure oxygen distributions in many human cancers, including the breast,[12] head and neck,[2–4] cervix,[5] and brain.[13] These studies were performed with standard 7 to 8-cm-long microelectrodes and demonstrated that oxygen levels in human tumors are heterogeneous but, on average, significantly lower than those in normal tissues. To date, no in vivo electrode measurements of oxygen levels in prostate cancer have been reported.

Several studies have examined the issue of oxygenation of prostate tumors in animal models.[10,11] Using the Eppendorf probes, Yeh *et al.*[10] found that the pO_2 values of anaplastic Dunning rat prostatic tumors were significantly lower than those of well differentiated tumors; pO_2 levels in both tumors were significantly lower than those measured in normal rat muscle. Only a few studies, with only a handful of patients, have reported on the oxygenation status of human prostate cancer,[7–9] and none have used the Eppendorf microelectrode. These novel radiodiagnostic assays of tumor hypoxia require validation and correlation with other assays, especially the electrode procedures.[14] For example, using positron emission tomography after injection of the hypoxic marker, [^{18}F]fluoromisonidazole, Rasey *et al.*[9] observed hypoxia in 36 of 37 tumors and in all 4 of the prostate cancers studied.

The current report, to our knowledge, represents the first study to obtain in vivo electrode measurements of oxygen levels in patients with prostate carcinoma. They were made possible by the customized manufacture of 12 to 14-cm-long microelectrodes by Eppendorf in response to our request. The results, incorporating 2145 separate pO_2 measurements, suggest that hypoxic regions exist in human prostate carcinoma. Because of the differences in patient characteristics and the type of anesthesia employed, we obtained control measurements from a region of normal muscle as an internal control in all but 2 patients. This internal comparison showed statistically significant differences in the oxygen measurements between the "involved" portion of the prostate versus a region of normal muscle (Table I). As well, the relatively high pO_2 readings from the pathologically normal prostate (in the 2 patients with bladder cancer) compared with those in patients with prostate carcinoma preliminarily suggest that it is not the prostate itself that is hypoxic but rather the presence of the cancer in the prostate that leads to "hypoxic regions."

The type of anesthesia is known to affect pO_2 readings obtained with the Eppendorf microelectrodes. In animal tumors, measurements obtained under fluorine-based anesthesia yield higher pO_2 readings than measurements obtained under normal air-breathing conditions (Chapman JD, personal communication, July 1998). As expected, the type of anesthesia in the present study did have an independently significant impact on the pO_2 measurements. For this reason, one may not be able to reliably compare the measurements taken from patients undergoing surgery and those undergoing brachytherapy.

Multivariate analysis of all 12 patients showed that the interaction of the type of tissue (prostatic versus muscle) and the type of cancer (prostate versus bladder) was a significant predictor of oxygen measurements ($P = 0.0001$). Modeling of the 10 patients with prostate cancer showed that the significant predictors of oxygenation include the type of tissue (prostatic versus muscle, $P < 0.0001$), clinical stage ($P = 0.001$), and type of anesthesia ($P = 0.002$). When controlling for the type of tissue, the significant predictors of oxygenation in the pathologically involved prostatic tissue included clinical stage ($P = 0.004$) and type of anesthesia ($P = 0.03$). Although the impact of Gleason score could not be evaluated in the present study, the heterogeneity of the pO_2 measurements in tumors with similar Gleason scores is interesting. The ultimate purpose of the present prospective study is to correlate the oxygenation status of prostate carcinoma with known prognostic factors and treatment outcome. Additional patients will be required for that purpose. These results could eventually be correlated with noninvasive techniques that indicate tumor oxygenation, such as magnetic resonance spectroscopy or appropriate nuclear medicine markers.[14]

The prognostic implications of the current study are potentially far-reaching. Local failure remains an important problem in the treatment of prostate cancer, particularly in patients with locally advanced disease. Pilepich *et al.*[15] found that when the product of the dimensions of the palpable tumor exceeded 25 cm^2, the local failure rate after radiation at 6 years was higher than 50%, compared with 25% or less for smaller lesions. The biologic finding of increased levels of hypoxia with increasing clinical stage (Fig. 3) suggests that hypoxia may be a factor underlying the higher rate of treatment failure in patients with locally advanced disease. It is estimated that approximately 40% of all patients with prostate cancer present with locally advanced disease.[16] Although standard therapy for such patients has historically been external beam radiotherapy, this treatment has yielded disappointing results, with 10 and 15-year survival rates of only 33% and 23%, respectively.[17] Recently, strategies have focused on the addition of hormonal therapy,[18] neutron therapy,[19] and dose escalation in the context of three-dimensional con-

formal radiotherapy[20] and/or brachytherapy.[21] We previously demonstrated a significant benefit in biochemical freedom from disease control to radiation dose escalation in patients with PSA levels greater than 10 ng/mL,[22] and, more recently, in patients with lower PSA levels as well.[23] Moreover, Radiation Therapy Oncology Group Trial 86-10 demonstrated a significant improvement in disease-free survival and biochemical freedom from disease control in patients with locally advanced prostate cancer with the addition of hormonal therapy to radiotherapy.[18] The relative merits of such strategies may ultimately correlate with their individual success in combating hypoxia-induced treatment failure.

The oxygenation status of tumors in individual patients has been previously correlated with outcome after radiotherapy. Höckel *et al.*[5] showed that patients with cervical cancer whose median pO_2 was 10 mm Hg or higher had significantly higher rates of tumor response and improved survival after radiotherapy than patients with tumors of pO_2 levels less than 10 mm Hg. Of interest, the averages of the median pO_2 levels in patients with clinical Stage T2A and T2B disease in the present study were less than 10 mm Hg, which may be clinically significant. We hypothesize that the presence of such hypoxic regions in some prostate carcinomas will inversely correlate with outcome measurements of local control and biochemical freedom from disease. Similar outcome results have been reported in patients with head and neck cancers.[2–4] These studies suggest that the pO_2 microelectrode histograph may be used to select patients most likely to benefit from novel hypoxic-specific therapies.

Nevertheless, the majority of clinical trials with hyperbaric oxygen or hypoxic radiosensitizers have failed to show improved treatment response.[24] The review of Overgaard and Horsman[25] of the published data demonstrates that most studies individually lacked the statistical power to demonstrate a significant difference on the basis of treatment. A meta-analysis of these same studies showed that hypoxia-related strategies were associated with a significant improvement in both local regional control and survival.[25] Another fundamental problem with prior clinical investigations was that they were conducted with little or no knowledge of the oxygenation status of the tumors accessed by the studies. Hypoxic fractions of both rodent and human tumors are now known to vary widely.[26] This finding is corroborated by the relatively heterogeneous pO_2 readings seen in our patient cohort. Applying a hypoxic-specific therapy to all patients will undoubtedly dilute the benefit to tumors that have substantial hypoxic fractions.

Recently, new hypoxia-specific agents have been developed, such as Tirapazamine, a hypoxic cytotoxin. A key limiting factor in the effective application of hypoxic radiosensitizers in the past was a cumulative dose-related toxicity after administration of multiple dosages over an extended course of fractionated radiotherapy. A brachytherapy implant is potentially an ideal setting in which to use hypoxia-targeted therapy, in that high drug concentrations with fewer doses can be safely achieved during the course of the implant. Ultimately, the goal of such research will be to direct a hypoxic-specific therapy to those patients specifically identified to be at risk for poor outcome on the basis of oxygenation status. Such an innovative approach would represent a paradigm shift in our understanding and management of patients with prostate carcinoma.

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