Interstitial Hypertension in Carcinoma of Uterine Cervix in Patients: Possible Correlation with Tumor Oxygenation and Radiation Response

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Abstract

Elevated tumor interstitial fluid pressure (IFP) is believed to be responsible, at least in part, for the poor penetration and heterogeneous distribution of blood-borne therapeutic agents and nutrients in solid tumors. Using the wick-in-needle technique, IFP was measured in human patients with squamous cell carcinoma of the uterine cervix at the initial and final stages of fractionated external beam radiotherapy. Mean IFP values ranged from 10 to 26 mm Hg with an overall mean of 15.7 ± 5.7 (SD) mm Hg in stage IIB and IIIB tumors (n = 12) and from 0 to 3 mm Hg in normal cervix (n = 3). IFP decreased in some patients with therapy while in others it increased. The changes in IFP values agree well with the clinical response to radiotherapy (n = 7, P < 0.05). Oxygen tension, measured in selected tumors (n = 3) with polarographic oxygen microelectrodes, inversely correlated with IFP. These results show for the first time that the IFP in human cervical carcinomas is elevated, and that it can be lowered in some tumors using fractionated radiation therapy. These findings also suggest that IFP values may provide an indication of tumor oxygenation and that IFP modifications could be prognostic indicators of radiation response.

Introduction

The effectiveness of therapies currently in use for the treatment of solid tumors is limited by physiological resistance and by intrinsic or acquired cellular resistance. The former impedes the delivery of blood-borne therapeutic agents to tumors, and the latter reduces their effectiveness once these agents have reached the target cells. Physiological resistance stems primarily from heterogeneous blood supply and interstitial hypertension (1). Heterogeneous blood supply may limit the access of nutrients and systemically administered agents to well-perfused regions of a tumor. Interstitial hypertension may reduce the driving force for extravasation of fluid and macromolecules and may help “wash” these molecules from the tumor periphery into the surrounding normal tissue (2, 3). Despite the obvious importance of these concepts, there are no data on interstitial pressure in human tumors or on the strategies to modify it in patients.

In most normal tissues, the IFP is approximately zero mm Hg. Since the pioneering work of Young et al. (4), several investigators have shown that IFP is significantly elevated in experimental tumors and that it may increase with growth in some tumors (for review, see Refs. 3 and 5). Furthermore, we have shown theoretically (6) and verified experimentally (5) that in tumors with a single nodule, IFP is elevated and relatively uniform, except at the tumor-normal tissue interface where it rapidly falls to normal values. Therefore, random central IFP measurements may be representative of the entire tumor nodule. Whether these observations are true for human tumors in situ is not known. To this end, we have recently measured IFP in superficial malignant melanomas in cancer patients (7) using the wick-in-needle technique (8). These results show that IFP is indeed elevated in human melanomas and that IFP in large melanomas (7–41 mm Hg; mean ± SD, 23 ± 13) far exceeds that in any experimental tumor reported to date. Therefore, the primary objective of this study was to find out if carcinoma of the uterine cervix exhibit also high IFP values. Since we made these measurements in stage IIB and IIIB cervical carcinoma patients (n = 13) undergoing radiotherapy, we were able to explore possible correlations between IFP and cell differentiation (grade) or tumor response to therapy. Finally, to gain further insight into the etiology of interstitial hypertension in human tumors, we measured simultaneously the oxygen tension (pO₂) distribution in a limited number of patients (n = 3).

Materials and Methods

Patient Selection. IFP was measured in 13 patients with clinical stage IIB and IIIB squamous cell carcinoma of the uterine cervix who received treatment at the Magee-Womens Hospital in Pittsburgh between May 1990 and August 1991. All measurements were performed with the approval of the Institutional Review Board and written informed consent from each patient. The patients ranged in age from 31 to 75 years (49 ± 13). All patients were treated with curative intent. The cumulative external beam radiation dose to central pelvis was 39.6 to 60.0 Gy using a 6-Mev linear accelerator. Intracavitary insertion of 125I seeds (brachytherapy) was routinely added to external beam irradiation for a total dose of 85 to 95 Gy. External beam boosts to the parametria were added on an individual basis after brachytherapy.

IFP Measurements. The details of the wick-in-needle method are given in Ref. 8. In brief, a 23-gauge hypodermic needle (0.6 mm outside diameter) with a 3-mm diameter side hole located at 3–4 mm from the needle tip was filled with nylon surgical suture (6-0 ethilon) filaments. The filaments were exposed to the tissue through the elongated side hole. Polyethylene tubing (PE 50) filled with heparinized (70 units/ml) isotonic saline connected the needle to a pressure transducer (Model P23 ID; Gould Electronics, Cleveland, OH). The pressure signal was amplified (Model 11–4113-01; Gould Electronics), digitized (MacLab System; WPI, New Haven, CT), and stored. Measurements were made with patients in the dorsal lithotomy position. This positioned the tumor at approximately heart level, thus minimizing the difference in hydrostatic blood pressure. Calibration was checked and there was no change before and after the measurements. Under sterile conditions, the needle was inserted to a depth of at least 1.5 cm from the tumor surface and left in place without external fixation. Fluid communication...
INTERSTITIAL HYPERTENSION IN HUMAN TUMORS

was checked by compressing and decompressing the plastic tubing with a metal clamp. The mean pressure was calculated after compression and decompression. If these two values were within 1–2 mm Hg of each other, the measurement was considered valid. Whenever possible two measurements of IFP were made per tumor. Table 1 lists the mean of 2 IFP measurements whenever possible; otherwise a single IFP measurement is given. The relationship between changes in IFP and radioresponsiveness was analyzed with a χ² test using a 2 × 2 contingency matrix.

Oxygen Tension Measurements. Oxygen tension was measured using a commercially available 25-gauge polarographic microelectrode (Model 737; Diamond General, Ann Arbor, MI). The tip of each electrode contained a membranized recessed cathode 25 μm in diameter. The electrode exhibited a mean oxygen sensitivity of 2.5–3.0 pa/mm Hg when placed in isotonic saline at 37°C. The oxygen electrode was polarized by applying a constant voltage (−0.7 V) and calibrated at 37°C in isotonic saline containing known amounts of oxygen (0, 4, 8 weight %). The cathode was introduced to the depth corresponding to one-half of the size of the tumor. After allowing 10–15 min for the electrode to stabilize, it was withdrawn in a stepwise manner using a hydraulic micropositioner (Model 650; David Kopf Instrument, Tujunga, CA), and the measured currents were amplified (Model 614 Electrometer; Keithley, Cleveland, OH) and recorded. The data were digitized (MacLab System) and displayed on a monitor screen. These measurements were made in a single track per tumor. The pO₂ profile was calculated from the measured currents using the calibration line. The calibration was within ±5% before and after measurements. The relative frequency of pO₂ was calculated and its histogram was drawn.

Due to the length of the procedure, patient discomfort while in the lithotomy position was a limiting factor. To minimize perturbations, IFP and pO₂ measurements were made without local anesthesia. Determinations of IFP alone were faster, taking less than 30 min to complete, but simultaneous IFP and pO₂ measurements took an extended period of 60 min or more, which accounts for our ability to measure both in only three patients.

Results

The IFP values in 13 patients are shown in Table 1. IFP was also obtained for normal uterine cervix in three patients and found to be between 0 and 3 mm Hg. The first IFP measurement (IFP1) was obtained after the bleeding from the tumor was controlled by radiation, usually with doses lower than 7.2 Gy (except in two patients who required 14.4 and 19.8 Gy). The second determination (IFP2) was made after 30 Gy.

Tumor regression was recorded at 20 Gy, 40 Gy, and at the first follow-up visit, 4 to 6 weeks after completion of radiation therapy (Table 1). Values given were 0 for no response (less than 25% reduction in estimated tumor volume), 1 for minimal response (between 25 and 50% reduction), 2 for moderate response (greater than 50% reduction), and 3 for complete response (no tumor felt or seen on examination).

Table 1 IFP in cervical carcinomas during radiation therapy

<table>
<thead>
<tr>
<th>Age</th>
<th>Stage</th>
<th>Histology</th>
<th>Grade</th>
<th>IFP1 (mm Hg)</th>
<th>IFP2 (mm Hg)</th>
<th>BP* (mm Hg)</th>
<th>Response at 20 Gy</th>
<th>Response at 40 Gy</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/75</td>
<td>IIIB</td>
<td>AC</td>
<td>WD</td>
<td>24 (5.4)</td>
<td>0 (37.5)</td>
<td>134/80</td>
<td>0–1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>B/39</td>
<td>IIIB</td>
<td>SCC</td>
<td>MD</td>
<td>12 (5.4)</td>
<td>7 (43.2)</td>
<td>146/62</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>C/45</td>
<td>IIIB</td>
<td>SCC</td>
<td>MD</td>
<td>21 (3.6)</td>
<td>2 (39.6)</td>
<td>100/60</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>D/31</td>
<td>IIIB</td>
<td>SCC</td>
<td>PD</td>
<td>10 (7.2)</td>
<td>3 (39.6)</td>
<td>na</td>
<td>1–2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>E/50</td>
<td>IIIB</td>
<td>SCC</td>
<td>MD</td>
<td>10 (3.6)</td>
<td>20 (32.0)</td>
<td>120/78</td>
<td>0</td>
<td>0</td>
<td>d</td>
</tr>
<tr>
<td>F/53</td>
<td>IIIB</td>
<td>AS</td>
<td>PD</td>
<td>12 (7.2)</td>
<td>25 (46.8)</td>
<td>110/70</td>
<td>0–1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>G/49</td>
<td>IIIB</td>
<td>SCC</td>
<td>WD</td>
<td>20 (6.0)</td>
<td>21 (60.0)</td>
<td>160/96</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>H/64</td>
<td>IIIB</td>
<td>SCC</td>
<td>MD</td>
<td>12 (3.6)</td>
<td>31 (39.6)</td>
<td>170/90</td>
<td>0–1</td>
<td>0–1</td>
<td>2</td>
</tr>
<tr>
<td>I/74</td>
<td>IIIB</td>
<td>SCC</td>
<td>PD</td>
<td>26 (0.0)</td>
<td>26 (0.0)</td>
<td>150/80</td>
<td>0</td>
<td>0</td>
<td>na</td>
</tr>
<tr>
<td>J/41</td>
<td>IIIB</td>
<td>SCC</td>
<td>PD</td>
<td>11 (5.4)</td>
<td>124/100</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>K/49</td>
<td>IIIB</td>
<td>SCC</td>
<td>MD</td>
<td>16 (19.8)</td>
<td>90/60</td>
<td>1–2</td>
<td>1–2</td>
<td>1–2</td>
<td>e</td>
</tr>
<tr>
<td>L/44</td>
<td>IIIB</td>
<td>SCC</td>
<td>MD</td>
<td>14 (11.4)</td>
<td>118/74</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>M/38</td>
<td>IIIB</td>
<td>SCC</td>
<td>PD</td>
<td>31 (39.6)</td>
<td>108/70</td>
<td>1–2</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

* BP, blood pressure; AC, adenoscarcoma; SCC, squamous cell carcinoma; AS, adenosquamous cell carcinoma; WD, well differentiated; PD, poorly differentiated; na, not available; nm, not measured due to technical difficulties such as poor fluid communication; d, died of disease; e, not determined yet; 0, no response (less than 25% reduction in estimated tumor volume); 1, minimal response (between 25 and 50% reduction); 2, moderate response (greater than 50% reduction); 3, complete response (no tumor felt or seen on examination).

Numbers in parentheses, cumulative dose at the time of IFP measurements.
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An interesting and novel observation in the current investigation is that fractionated radiation lowers IFP in some tumors. We had proposed that lowering of IFP due to fractionated radiation therapy is at least partially responsible (1–3) for enhanced delivery of monoclonal antibodies to tumors (15–17). While the mechanism(s) of this pressure reduction and why pressure goes down in some tumors and not in others are not completely understood, measurements of IFP can help identify specific therapy for individual tumors and can be used to design strategies to increase the delivery of antibodies and other macromolecules made from genetic engineering.

Current prognostic indicators for radiation therapy in patients include pO2 distribution (18), malignancy grading (19, 20), intrinsic cellular radiosensitivity (21), and tumor regression (22, 23). Therefore, the possible correlation between IFP and tumor grade and between changes in IFP and tumor response to therapy, if confirmed in a large number of patients, may be useful in predicting treatment outcome and in determining future strategies for treatment. In fact, a similar correlation between changes in IFP and treatment outcome for hyperther-

Discussion

The primary goal of this study was to determine IFP in human cervical carcinomas in situ. Our results show that these tumors do exhibit interstitial hypertension. These IFP values are comparable to those in transplanted rodent tumors (3, 5), in human tumor xenografts (9), and in human primary and metastatic breast and colorectal tumors (10) as well as in tumors of the head and neck region also measured in situ. They are, however, lower than those in large human melamomas (7). Whether the lower values are due to histological and size differences or to the fact that all cervical carcinomas (except patient I with IFP = 26 mm Hg) were treated with low dose radiation to control bleeding prior to the first IFP measurement is not known. Further human studies are in progress to resolve this issue.

Since the pioneering studies of Gullino, it is known that in transplanted rodent tumors, the perfusion rate generally decreases with tumor growth (for review, see Refs. 11 and 12). IFP is also known to increase with growth in some rodent tumors (3, 5). Therefore, it seems reasonable to expect an inverse relationship between IFP and perfusion rate, at least in some tumors. Since the oxygen availability and consumption and, hence, pO2 distribution in a tumor are governed by its perfusion rate (11, 13), we hypothesized that pO2 and IFP may also be inversely related, at least in some tumors. We have indeed found this to be true in some human tumor xenografts (9). To test this possibility in human tumors, we made simultaneous pO2 and IFP measurements in three patients. These preliminary studies are in concert with our hypothesis. Furthermore, our pO2 values agree with recent data on pO2 distributions in human cervical carcinomas (14). IFP measurements are considerably easier to perform than detailed pO2 distributions or local blood flow rates throughout the tumor. Therefore, if our hypothesis is validated based on additional human data, it will have immediate and useful implication for individualizing cancer therapy.

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Fig. 2. Relationship between cell differentiation and IFP1 values. Cell differentiation is graded as follows: poor, moderate, well differentiated = 3, 2, 1, respectively (\( y = 28 - 6.2x, R^2 = 0.647, P < 0.05 \)). Note that these preliminary results suggest that IFP may increase with the degree of differentiation of cervical carcinoma.

Fig. 3B depicts the pO2 distribution in these patients (B, G, and D). Patients B and G had IFP2 values of 7 and 21 mm Hg, respectively, and patient D had an IFP1 value of 10 mm Hg at the time of the pO2 measurements.

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mia in rodent tumors has been recently observed by us (24).

In summary, we have shown clearly that human cervical carcinomas have elevated IFP and that the IFP may be lowered in some tumors during fractionated radiation therapy. Our initial observations on possible relationships (a) between IFP and tumor grade or pO2 distribution and (b) between changes in IFP and therapeutic outcome are potentially useful and warrant further investigation.

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References

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