[CANCER RESEARCH 52, 1993–1995, April 1, 1992]

Advances in Brief

Interstitial Hypertension in Head and Neck Tumors in Patients: Correlation with Tumor Size[1]

Ralph Gutmann,[2] Michael Leunig, Jens Feyh, Alwin E. Goetz, Konrad Messmer, Ernst Kastenbauer, and Rakesh K. Jain[2]

Ear-Nose-Throat Clinic [R. G., J. F., E. K.], Institute for Surgical Research [M. L., K. M.], Institute for Anesthesiology [A. E. G.], University of Munich, Klinikum Grosshadern, Marchioninistrasse 15, 8000 Munich 70, Germany; and Steele Laboratory, Department of Radiation Oncology, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts 02114 [M. L., R. K. J.]

Abstract

Elevated interstitial fluid pressure (IFP) is associated with poor blood supply and inadequate delivery of drugs to solid tumors. IFP was measured in squamous cell carcinomas of the head and neck region in humans using the wick-in-needle technique. In all lesions ($n = 19$), the IFP was elevated (4–33 mm Hg). Furthermore, the IFP increased with tumor size. The highest IFP was 33 mm Hg in a 24-ml tumor. In one tumor, the IFP was found to be negative (−2.6 mm Hg), which is comparable to that in human skin or subcutaneous tissue. The histopathology of this tumor was benign. If this pressure difference between malignant and benign lesions can be confirmed in a large number of tumors, then the IFP could be used to aid tumor detection during needle biopsy. The value of IFP as a predictor of response to radiotherapy, photodynamic therapy, hyperthermia, and chemotherapy should be assessed prospectively.

Introduction

IFP[3] is approximately 0 mm Hg in most normal tissues. However, in solid tumors in animals the pressure has been shown to be elevated and to increase with tumor growth (1, 2). Furthermore, we have shown theoretically (3, 4) and verified experimentally (5) that in tumors growing as a single nodule, IFP is relatively uniform throughout the tumor, and it drops precipitously at the tumor-normal tissue interface. We have recently initiated a study of interstitial pressure in human tumors. To date, we have found that superficial malignant melanomas, cervical carcinomas, mammary carcinomas, and colorectal cancers have pressures comparable to those found in experimental tumors (6–8). The only surprising finding is that large malignant melanomas exhibit pressures which are considerably higher than those in any experimental or human tumors reported to date. Furthermore, we have found that in cervical carcinomas, IFP is correlated with cell differentiation and with tumor oxygenation (7). The objectives of the current study were to find out (*a*) if the head and neck tumors also exhibit interstitial hypertension comparable to other human tumors and (*b*) if the pressure increases with tumor growth. These studies were carried out using the wick-in-needle technique of Fadnes *et al.* (9) utilized in other human studies.

Received 12/12/91; accepted 2/18/92.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

[1] Supported by Bundesministerium für Forschung und Technik Grant 0706903A5 to A. E. G. and National Cancer Institute Grants CA37239 and CA49792 to R. K. J.; M. L. is the recipient of a Feodor-Lynen Fellowship (1991–1992); and R. K. J. was a recipient of a Humboldt Senior Scientist Award (1990–1991). This is the third paper in a series on interstitial pressure in human tumors.

[2] To whom requests for reprints should be addressed.

[3] The abbreviation used is: IFP, interstitial fluid pressure.

Materials and Methods

Patient Selection and Protocol. The study protocol was approved by the Institutional Review Board of the University of Munich. All patients signed a written consent. Measurements were made in the easily accessible tumors of ear, nose, and throat patients at Klinikum Grosshadern, Ludwig-Maximilians-University Munich, prior to therapy. Tumors of the lip, tongue, palate, and nose as well as tumor metastases in the neck region were included in this study.

All tumors were of known pathology except one: 16 tumors were squamous cell carcinomas (7 primary and 9 metastasis), 3 were primary spinocellular carcinomas, and one was benign fibrous tissue. All tumors were examined by computed tomography or nuclear magnetic resonance. The tumor size was measured with these imaging methods, and the volume was calculated as:

$$3.1415 \text{ (Length} \times \text{width} \times \text{height)} \div 6$$

IFP Measurement System. The IFP measurements were made using the "wick-in-needle" technique (9). Briefly, a 2- to 4-mm-long side hole was made in the needle about 4 mm from the tip. Multifilamentous nylon fibers were pulled into the needles, and the needles were connected to a polyethylene tube. The distal end of the tube was connected to the dome of a pressure transducer (Statham; Gould, Oxnard, CA). A screw clamp allowed compression and decompression of the tube to determine fluid communication. The whole system was filled with sterile saline. The pressure was measured and recorded with a pressure amplifier (Pressure Amplifier 836; Siemens, Elema, Sweden) and recorder (Kompensograph X-T; Siemens, Munich, Germany), usually with a sensitivity of 2.0 mm of deflection/0.735 mm Hg. Zero reference was obtained by placing the needle in a sterile saline drop at tumor height. Calibration was done with a Gauer pressure calibration system. For pressure measurements the surface of the tumor was anesthetized with tetracain, and a gas-sterilized wick-in-needle was inserted into the tumor. The needles were usually inserted by means of forceps and left in place without fixation. After the insertion of the needle into the tumor, the pressure rose rapidly and stabilized at its final level within 3 to 10 min. [Note that the response time of the needles was slower than those reported by Boucher *et al.* (6) and Roh *et al.* (7). This difference is presumably due to the use of multifilamentous nylon wick as described by Fadnes *et al.* (9) instead of six single fibers as used by the above-mentioned authors (6, 7).] After stabilization of the pressure, the screw clamp was tightened so as to inject a small volume of saline into the tumor. This caused a sudden increase of the pressure, which declined in the following 2 or 3 min. Loosening the clamp showed an inverse response with final return to the original level. The pressure response as described above confirmed good fluid communication and the validity of the measurement. Bleeding was rare and was recognized by a continuously rising pressure. The duration of one measurement of IFP was about 15 min. Systolic and diastolic blood pressure before and after the insertion of the needle was measured every 3 min in the upper arm of the patients (Riva Rocci).

Downloaded from http://aacrjournals.org/cancerres/article-pdf/52/7/1993/2450416/cr0520071993.pdf by guest on 15 April 2024

Results

Blood pressure measured before and during IFP measurements did not change significantly and was stable during measurements. Table 1 shows the blood pressure and IFP, along with the histopathological parameters. There was no significant correlation between the blood pressure and the IFP. The blood parameters (determined by clinical routine methods), especially the osmolarity, were in the normal range.

All squamous cell carcinomas exhibited interstitial hypertension. The IFP ranged from 4 to 33 mm Hg. Furthermore, the IFP increased significantly with tumor size (Fig. 1). The highest IFP measured was 33 mm Hg in a tumor with a volume of 24 ml. There was a good correlation between IFP and tumor volume ($R_{Spearman} = 0.79$; $P < 0.001$). No correlation was found between blood pressure and IFP ($R_{Spearman} = 0.27$; $P < 0.26$). However, no attempt was made to modulate systemic blood pressure to study its effect on IFP.

IFP was measured in one tumor without knowledge of its histopathology prior to measurement. It appeared as a subcutaneous tumor of the nose. The IFP was negative (−2.6 mm Hg), and the postoperative histopathology confirmed it to be benign fibrous tissue. This case is not included in Fig. 1.

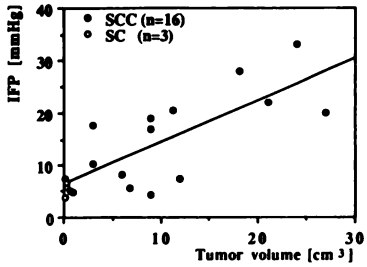

Fig. 1. Correlation between the volume and the IFP of malignant tumors. ●, squamous cell carcinomas (SCC); ○, spinocellular carcinomas (SC). Note that tumors of all locations, stage, and grade are shown. With increase in tumor volume, tumor IFP increased significantly ($R_{Spearman} = 0.79$; $P < 0.001$).

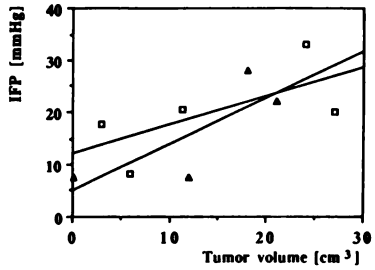

Fig. 2. Correlation between the volume and the IFP of metastasis of different grades. There is a tendency toward a steeper IFP rise with increase in tumor volume for metastasis of grade 3 (▲) compared to grade 2 (□).

Discussion

The objective of this study was to measure the IFP in the head and neck tumors in patients. Our results show that these tumors exhibit interstitial hypertension values comparable to those in transplanted rodent tumors, in human tumor xenografts, and in human primary and metastatic tumors. Specifically, these values of squamous cell carcinomas in the head and neck region are comparable to those found in the cervical region in another study (7). However, these values are lower than those in large human melanomas (6). Whether the lower values are due to histological or size differences is not known.

The second goal of the study was to determine the relationship between interstitial pressure and the tumor size. Although Boucher *et al.* (6) have shown that large melanomas have pressures higher than those of smaller melanomas, their limited sample size did not allow the determination of the quantitative dependence on tumor weight. The present study shows clearly that in the tumor size range of up to 24 ml volume, the interstitial pressure rises similar to that observed in several experimental tumors (1, 5, 10–13). Similar studies with a large number of patients are now needed to define tumor weight dependence in other tumor types.

The third objective of this study was to relate interstitial pressure with the tumor grade (differentiation). In squamous cell carcinoma of the uterine cervix region, the IFP increased with the grade (degree of differentiation) of tumors in a significant manner (7). Although there was a tendency for a steeper pressure increase with weight in grade 3 compared to grade 2 metastasis (Fig. 2), we did not find a significant difference for the tumors of the head and neck region. This may be related to the different locations of the tumors (lip, tongue, palate) and metastasis. However, it was interesting to find normal tissue interstitial pressure in a benign lesion. If this pressure difference between malignant and benign lesions can be confirmed in a large number of tumors, then the IFP could be used to detect malignant tumors during needle biopsy.

In a separate study, we have demonstrated that the interstitial pressure can be lowered in experimental and human tumors using fractionated radiotherapy or hyperthermia (7, 14). Furthermore, we have found that the change in interstitial pressure correlated with the outcome of therapy. Similar studies are now needed in tumors of the head and neck region undergoing chemotherapy, photodynamic therapy, or radiotherapy. These studies will help in developing strategies to lower the pressure for improved delivery of novel therapeutic agents (15).

Table 1 *Interstitial pressure in head and neck tumors*

Age/sex	Tumor volume (cm^3)	Tumor location	Stage	Grade	Blood pressure (mmHg)	IFP (mmHg)
Squamous cell carcinomas						
77/F	0.7	Tongue	T1N0M0	G2	125/75	5
65/M	0.9	Tongue	T1N0M0	G2	160/90	4
60/M	9.0	Tongue	T3N0M0	G2	125/90	17
59/F	1.0	Palate	T1N0M0	G2	165/90	5
73/M	3.0	Palate	T2N2M0	G3	140/85	10
54/M	6.8	Lip	T4N2Mx	G2	155/95	6
87/M	9.0	Lip	T3NxMx	G2	130/80	19
76/F	0.1	Metastasis	T2N2M1	G3	110/65	9
64/M	3.0	Metastasis	T4N1M1	G2	100/70	18
64/M	6.0	Metastasis	T4N1M1	G2	100/60	8
64/M	11.3	Metastasis	T4N1M1	G2	100/70	21
76/F	12.0	Metastasis	T2N2M1	G3	115/70	8
73/M	18.0	Metastasis	T2N2M0	G3	140/80	28
53/M	21.0	Metastasis	T4N2Mx	G3	100/70	22
55/M	24.0	Metastasis	T3N2M0	G2	120/90	33
54/M	27.0	Metastasis	T4N2Mx	G2	145/85	20
Spinocellular carcinoma						
59/M	0.2	Lip	T1N0M0		110/70	4
59/M	0.3	Lip	T1N0M0		115/75	6
75/F	0.3	Lip	T1N0M0		155/80	7
Fibrous tissue						
42/F	0.3	Nose			135/80	−3

Acknowledgments

We thank Drs. Yves Boucher, Herman D. Suit, C. C. Wang, and Wlodzimierz Ruka for their helpful comments on this manuscript.

Downloaded from http://aacrjournals.org/cancerres/article-pdf/52/7/1993/2450416/cr0520071993.pdf by guest on 15 April 2024

References

1. Young, J. S., Lumsden, C. E., and Stalker, A. L. The significance of the "tissue pressure" of normal testicular and of neoplastic (Brown-Pearce carcinoma) tissue in the rabbit. J. Pathol. Bacteriol., *62:* 313–332, 1950.
2. Jain, R. K. Transport of molecules in the tumor interstitium: a review. Cancer Res., *47:* 3039–3051, 1987.
3. Jain, R. K., and Baxter, L. T. Mechanisms of heterogenous distribution of monoclonal antibodies and other macromolecules in tumor: significance of elevated interstitial pressure. Cancer Res., *48:* 7022–7032, 1988.
4. Baxter, L. T., and Jain, R. K. Transport of fluid and macromolecules in tumors. I. Role of interstitial pressure and convection. Microvasc. Res., *37:* 77–104, 1989.
5. Boucher, Y., Baxter, L. T., and Jain, R. K. Interstitial pressure gradients in tissue-isolated and subcutaneous tumors. Cancer Res., *50:* 4478–4484, 1990.
6. Boucher, Y., Kirkwood, J. M., Opacic, D., Desantis, M., and Jain, R. K. Interstitial hypertension in superficial metastatic melanomas in humans. Cancer Res., *51:* 6691–6694, 1991.
7. Roh, H. D., Boucher, Y., Kalnicki, S., Buchsbaum, R., Bloomer, W. D., and Jain, R. K. Interstitial hypertension in carcinoma of uterine cervix in patients: possible correlation with tumor oxygenation and radiation response. Cancer Res., *51:* 6695–6698, 1991.
8. Less, J. R., Posner, M. C., Boucher, Y., Wolmark, N., and Jain, R. K. Elevated interstitial fluid pressure in human tumors. Proc. Am. Assoc. Cancer Res., *32:* 59, 1991.
9. Fadnes, H. O., Reed, R. K., and Aukland, K. Interstitial fluid pressure in rats measured with a modified wick technique. Microvasc. Res., *14:* 27–36, 1977.
10. Wiig, H., Tveit, E., Hultborn, R. K., and Weiss, L. Interstitial fluid pressure in DMBA-induced rat mammary tumors. Scand. J. Clin. Lab. Invest., *42:* 159–164, 1982.
11. Hori, K., Suzuki, M., Abe, I., and Saito, S. Increased tumor tissue pressure in association with the growth of rat tumors. Jpn. J. Cancer Res., *77:* 65–73, 1986.
12. Paskins-Hurlburt, A. J., Hollenberg, N. K., and Abrams, H. L. Tumor perfusion in relation to the rapid growth phase and necrosis: studies on the Walker carcinoma in the rat testicle. Microvasc. Res., *24:* 15–24, 1982.
13. Misiewicz, M. A. Microvascular and interstitial pressure in normal and neoplastic tissues. (Master's thesis), Carnegie Mellon University, Pittsburgh, 1986.
14. Leunig, M., Goetz, A. E., Dellian, M., Zetterer, G., Gamarra, F., Jain, R. K., and Messmer, K. Interstitial fluid pressure in solid tumors following hyperthermia: possible correlation with therapeutic response. Cancer Res., *52:* 487–490, 1992.
15. Jain, R. K. Delivery of novel therapeutic agents in tumors: physiological barriers and strategies. J. Natl. Cancer Inst., *81:* 570–576, 1989.

Downloaded from http://aacrjournals.org/cancerres/article-pdf/52/7/1993/2450416/cr0520071993.pdf by guest on 15 April 2024