

Oxygenation of Carcinomas of the Uterine Cervix: Evaluation by Computerized O₂ Tension Measurements

M. Höckel, K. Schlenger, C. Knoop, and P. Vaupel¹

Department of Obstetrics and Gynecology [M. H., C. K.] and Institute of Physiology and Pathophysiology [K. S., P. V]), University of Mainz, Duesbergweg 6, D-6500 Mainz, Germany

ABSTRACT

Direct oxygen partial pressure (pO₂) readings in cancers of the cervix and in the normal cervix of nulliparous or parous women were obtained using a computerized pO₂ histography system. The oxygenation status of the tumors was evaluated as a function of clinical staging and histological grading. pO₂ measurements were performed with a customized electrode system in conscious pre- and postmenopausal, untreated patients with well-defined arterial blood gas status.

With this technique, pO₂ measurements in the normal cervix of nulliparous women resulted in oxygenation patterns which were characteristic for normal, adequately supplied tissues (median pO₂, 48 mm Hg) with approximately 1% of the pO₂ values grouped between zero and 2.5 mm Hg, *i.e.*, in a range with less than half-maximum radiosensitivity. As a rule, the mean (and median) pO₂ values were distinctly lower in the normal cervix of parous women (most probably due to scar formation following vaginal delivery) and in malignancies. In the normal cervix of parous women the median pO₂ value was 13 mm Hg (with approximately 14% of the pO₂ readings in the lowest class), 14 mm Hg in International Federation of Gynecologists and Obstetricians I/II tumors (2% of the readings in the lowest pO₂ class), and 11 mm Hg in International Federation of Gynecologists and Obstetricians III/IV cancers (1% of the pO₂ data in the lowest class). To date, 5 of 18 cervical cancers exhibited pO₂ values between zero and 2.5 mm Hg. The oxygenation pattern in cervical cancers and the occurrence of hypoxia and/or anoxia did not correlate with either the clinical stages and histological grades or with a series of clinically relevant parameters (*e.g.*, tumor size). No significant differences were found between pre- and postmenopausal tumors, between squamous cell carcinomas and adenocarcinomas, and between endophytic or exophytic tumors.

From these studies there is clear indication that the oxygenation status of individual tumors cannot be predicted on the basis of staging and/or grading, predominantly because of the pronounced tumor-to-tumor variabilities. Evaluation of the tissue oxygenation of individual tumors is thus mandatory to prove that tumor oxygenation can predict the overall prognosis and/or treatment outcome.

INTRODUCTION

It has recently been shown that the oxygenation pattern in human breast cancers and the occurrence of hypoxia and/or anoxia does not correlate with either the pathological stages or the histological grades of the tumors investigated (1). In earlier studies Kolstad (2, 3) demonstrated a correlation between the mean and lowest observed tissue oxygen tensions and the stage of disease in superficial regions of cervical cancers. Furthermore, Kolstad's data suggested that an association existed between large intercapillary distances, local recurrence and clinical staging. The latter finding has been confirmed by Awwad *et al.* (4) and by other investigations emphasizing the predictive value of the vascular density (which may reflect the tumor oxygenation) for survival after radiotherapy (5-8).

Thus far, pO₂ values determined in cervical cancers cannot be considered correct on an absolute scale (3, 9-12). Artifacts

due to large electrodes and thus tissue compression (11), problems with the calibration of the sensor (10), and the use of bare electrodes (9, 10, 12) are obvious in the earlier studies. Bare sensors monitor O₂ concentrations instead of O₂ partial pressures (O₂ tensions). For the evaluation of oxygen tension (pO₂) distribution in tissues, membrane-covered O₂ sensors are required (13). A direct conversion of O₂ concentrations (cO₂) into pO₂ values according to the Henry-Dalton law (cO₂ = $\alpha \cdot pO_2$) is not possible, since the O₂ solubility coefficient (α) is anisotropic in tissues (14). In addition, the validity of the O₂ data reported earlier is limited due to measurements in the tumor periphery only (3, 9-12) and due to a selection of patients with stage II malignancies (9-12). Reports on the oxygenation pattern of advanced malignancies are lacking. Furthermore, monitoring of the arterial blood gas status, which is mandatory for the evaluation of tissue oxygenation patterns, has not been performed in the earlier studies.

Reliable pO₂ readings in normal and malignant tissues are now possible using a novel, commercially available technique (computerized pO₂ histography) which allows for the systematic evaluation of the tissue oxygenation status. The measuring procedure uses a computerized O₂ sensor movement, minimizes compression artifacts, and has been shown to represent a valid method for analysis of tissue oxygenation patterns (for a recent description of this technique see Ref. 1).

Using this novel technique, the objective of this study was to investigate the oxygenation pattern in primary cancers of the uterine cervix in conscious patients, placing emphasis on a well defined arterial blood gas status and on the evaluation of the pO₂ distribution as a function of clinical staging and histological grading. Cervical carcinomas were selected as a tumor entity because radiation is a major treatment modality for this disease and tumor hypoxia is regarded an important factor for radioresistance in these tumors. In addition, accessibility of these malignancies allows systematic studies under clinical conditions.

The key questions were as follows: Do the pO₂ data obtained with this method match with earlier results suggesting low mean O₂ tensions or concentrations in cervical cancers? What are the absolute pO₂ values in cervical cancers as a function of clinical staging and histological grading? Are there differences in the oxygenation between squamous cell carcinomas and adenocarcinomas? Other key issues of this investigation were the comparison of the oxygenation pattern in normal cervical tissue and in malignancies, of the pO₂ distribution in the normal cervix of *para versus* nullipara, and the evaluation of O₂ patterns in central *versus* superficial tumor regions.

MATERIALS AND METHODS

Patients. As part of a prospective study on untreated patients with cancer of the uterine cervix which aims to assess the relevance of pO₂ measurements in individual tumors for local control after therapy, we have evaluated intratumor pO₂ measurements in 7 pre- and 11 postmenopausal conscious patients (age, 27-80 years) entering the study. Fifteen women presented with histologically confirmed squamous cell

Received 3/13/91; accepted 9/5/91.

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 To whom requests for reprints should be addressed.

carcinomas; 3 patients presented with adenocarcinomas. These patients were referred to the Department of Obstetrics and Gynecology, University of Mainz (Germany), for either surgical or irradiation treatment. None of the tumors had been treated previously. The relevant patient characteristics and tumor data are summarized in Table 1. Clinical staging according to the FIGO² classification (15) was performed independently by two experienced staff members. In case of disagreement with respect to parametrial tumor invasion, the patient was examined by a third staff member. For histological grading Broder's system was applied (16).

Cervical and/or cervical tumor diameters were measured during speculum examination. For determining the cervical (tumor) length in tumor patients, X-ray hystero-graphy was carried out with a surgical needle introduced into the outer surface of the portio. In addition, cervical (tumor) diameters were calculated from magnetic resonance imaging of the pelvis in coronal and sagittal planes. In healthy control subjects ($n = 14$; normal arterial blood gas status) cervical diameters were also measured during speculum investigation. Cervical lengths in the controls were determined by vaginasonography. Characteristics of control subjects are given in Table 2.

All patients and control subjects were fully informed about the experimental nature of the present investigation, gave consent without reservation, and experienced the absolute minimum of discomfort. In cancer patients, the tissue containing the electrode tracks was subsequently completely removed by ablative surgery or included into the target volume in the case of irradiation.

Measurements of Tissue Oxygen Tension Values with Needle Electrodes. For the measurement of tissue oxygen tension (pO_2) values, sterile polarographic needle electrodes with stainless steel shafts (of the hypodermic needle type) were used (pO_2 histography, model KIMOC-6650; Eppendorf, Hamburg, Germany). The probes had a shaft diameter of 300 μm . The sharply ground tips of the probes contained a membranized polarographic, recessed microcathode in the form of a gold wire 12 μm in diameter. Technical data for the needle electrodes, and a detailed description of the calibration procedure and of the data display have been given earlier (1). For the pO_2 measurements in uterine cervixes and cervical cancers, all patients and control subjects were placed in the lithotomy position. This positioning was consistently used throughout all measurements because changes of the leg position yield alterations in the pO_2 distribution in the pelvic organs (e.g., pO_2 values in the normal cervix of patients in the supine position with the lower legs below heart level are significantly lower than in patients placed in the lithotomy position³). Self-retracting specula were inserted into the vagina. In control subjects, the portio was positioned by means of a tenaculum in such a way that pO_2 measurements could be performed parallel to the cervical canal. In a pilot study, it was found that this positioning of the portio had no significant influence on the oxygenation pattern of the cervix. In cancer patients, pO_2 measurements were performed without positioning of the tumorous cervix due to the lack of the normal topography and the fixation of the tumor mass in the pelvis. The reference electrode was placed on the patient's left thigh.

In general, 2 defined electrode tracks were evaluated in each tumor, at the 12 and 6 o'clock positions, and 5 to 10 mm distal to the cervical canal or at the tumor margin. In some patients additional measurements were performed at the 2, 4, 8, and 10 o'clock positions. A plastic trocar (outer diameter, 0.8 mm) equipped with a hypodermic needle was advanced to an initial depth of approximately 2 mm. The hypodermic needle was then removed and the trocar was cut at 7 mm length so that it protruded 5 mm out of the tissue surface. The O_2 -sensitive electrode was guided through the trocar for tissue pO_2 measurements. pO_2 recordings in both peripheral and central tumor areas were performed in all electrode tracks chosen. This was confirmed by inspections of giant sections of surgical specimens in those patients undergoing radical hysterectomy.

The electrode was automatically moved through the tissue parallel to the cervical canal in preset steps of 1 mm. Each rapid forward

² The abbreviation used is: FIGO, International Federation of Gynecologists and Obstetricians.

³ Unpublished results.

Table 1 Characteristics of patients and cervical cancers undergoing computerized pO_2 histography

Age (yr)	Clinical staging (FIGO)	Histology	Histopathological grading	Maximum tumor diameter (cm)	Menopausal stage	Karnofsky index (%)	BP (mm Hg)	Heart rate (min ⁻¹)	Hemoglobin concentration (g/liter)	HbO ₂ saturation (sat. %)	Mean pO_2 (mm Hg)	Median pO_2 (mm Hg)	10 percentile (mm Hg)	90 percentile (mm Hg)	pO_2 readings between 0 and 2.5 mm Hg (%)
37	Ib	s.c.c. ^a	G2	2.0	Pre	100	140/90	91	128	98	26	14	9	56	0
47	Ila	s.c.c.	G2	5.0	Pre	100	130/90	88	135	100	17	10	5	43	0
27	Iib	s.c.c.	G3	5.0	Pre	100	120/80	87	127	100	22	16	3	50	6
41	Iib	s.c.c.	n.d.	6.0	Pre	100	140/85	90	151	97	31	26	8	75	0
56	Iib	s.c.c.	n.d.	5.5	Post	100	140/85	75	152	98	21	14	4	39	0
69	Iib	s.c.c.	G2	6.0	Post	90	180/90	72	121	98	13	4	2	51	13
69	Iib	s.c.c.	G2	>6.0	Post	90	150/90	72	99	99	38	22	18	90	0
76	Iib	ad.ca.	G2	3.0	Post	100	170/105	97	142	97	28	29	6	58	0
78	Iib	s.c.c.	G1	5.5	Post	90	160/95	90	102	96	29	11	6	75	0
80	Iib	s.c.c.	G2	5.5	Post	80	140/70	64	129	97	20	5	3	63	3
33	Iiib	s.c.c.	G2	>6.0	Pre	100	105/70	102	136	98	16	11	6	33	0
34	Iiib	ad.ca.	G1	10.0	Pre	100	130/85	68	n.d.	97	19	14	6	45	0
49	Iiib	s.c.c.	G2	8.0	Pre	80	135/90	100	n.d.	98	11	6	3	28	0
52	Iiib	s.c.c.	G2	7.0	Post	90	150/105	94	95	95	12	4	3	37	7
54	Iiib	s.c.c.	G2	6.0	Post	90	140/90	102	95	97	34	12	10	81	0
67	Iiib	s.c.c.	G2	8.0	Post	90	120/70	80	102	98	18	14	9	37	0
69	Iiib	s.c.c.	G2	3.0	Post	100	130/80	64	151	98	18	8	3	51	0
68	Iva	ad.ca.	G1	10.0	Post	100	150/85	60	148	100	6	5	10	10	1

^a BP, arterial blood pressure; HbO₂, arterial oxyhemoglobin saturation; s.c.c., squamous cell carcinoma; ad.ca., adenocarcinoma; n.d., not determined.

movement was immediately followed by a backward step of 30% of the forward motion in order to minimize compression effects caused by the forward motion of the O₂-sensitive needle electrode. This motion pattern led to an effective forward step length of maximally 0.7 mm. Depending on the tumor size, a sufficient number, *n*, of pO₂ readings (*n* > 50) were obtained in order to present the data by means of pO₂ frequency distributions (pO₂ histograms) which can reflect the oxygenation pattern of individual tumors.

The total length of the measuring canal corresponded to the length of the cervix or to the length of the cervical tumor if the latter did not exceed 40 mm. Otherwise a measuring length equal to one-half of the sagittal cervix/tumor diameter was used. At the end of the measurement the pO₂ probe was automatically removed from the tissue. In cancer patients the pO₂ measurements were carried out immediately before initiation of therapy. All measurements were conducted on conscious women not undergoing any cancer treatment.

Monitoring of Relevant Systemic Parameters. In order to guarantee that tissue pO₂ measurements were exclusively performed during arterial normoxemia, basic cardiovascular parameters (e.g., heart rate, arterial blood pressure) and factors determining the arterial O₂ concentration (e.g., hemoglobin concentration, hematocrit, arterial oxyhemoglobin saturation) were monitored during the measuring procedures (1).

Statistical Analysis. Using an on-line computing system, pO₂ histograms (i.e., pO₂ frequency distributions) were obtained with a class width of 2.5 mm Hg. The distribution of the measured pO₂ values was characterized by the mean pO₂, the median pO₂, and the 10 and 90 percentile values. For statistical evaluation of possible differences between groups the Mann-Whitney-Wilcoxon *U* test was used, if not stated otherwise.

RESULTS

Using the computerized pO₂ histography system, pO₂ values were recorded in the normal cervix of nullipara and para and in cancers of the uterine cervix of different clinical stages and histological grades. As a rule, the mean (and median) pO₂ values were distinctly lower in the malignancies and in the normal cervix of parous women than in the normal cervix of nulliparous women (see Figs. 1 and 2). The histograms for parous and nulliparous, healthy subjects were significantly different (*P* < 0.02). No differences in the oxygenation pattern of the normal uterine cervix were found between smokers and nonsmokers or users and nonusers of oral contraceptives.

In cancer patients, no differences in the pO₂ distribution were obvious between adenocarcinomas and squamous cell carcinomas; among endophytic (*n* = 4), exophytic (*n* = 8), and ulcerated tumors (*n* = 6); between para (*n* = 15) and nullipara (*n* = 3); or between pre- and postmenopausal patients. Pooled pO₂ histograms in cancer patients were similar to those obtained in the normal cervix of parous women. Thus far, 5 of 18 cervical cancers exhibited pO₂ values between zero and 2.5 mm Hg, i.e., tissue areas with less than half-maximum radiosensitivity. One of 7 normal cervixes in nulliparas and 3 of 7 cervixes in paras exhibited pO₂ values between zero and 2.5 mm Hg.

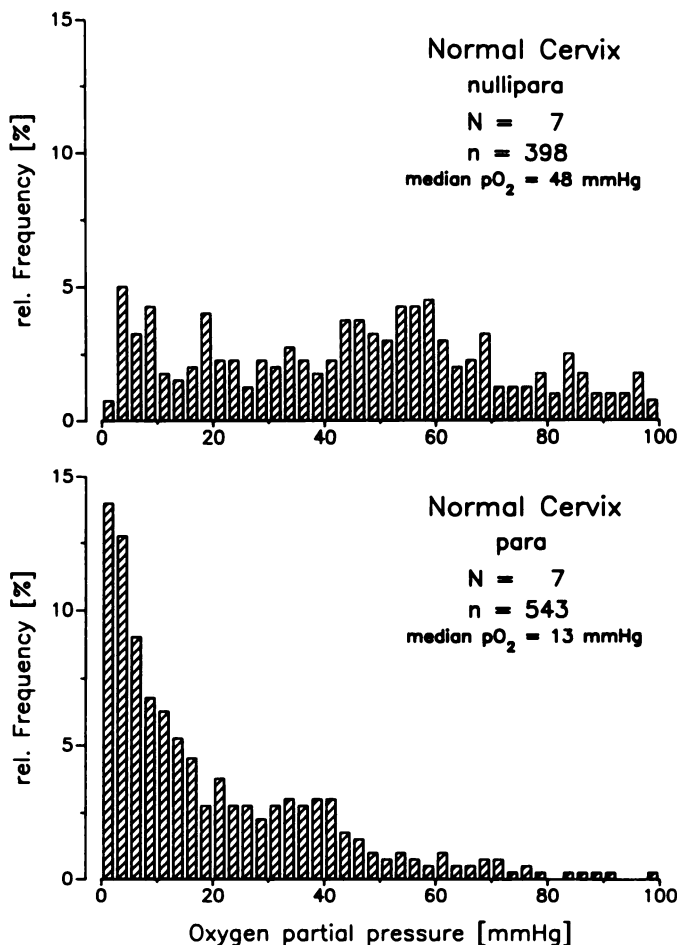


Fig. 1. Frequency distributions of measured oxygen partial pressures (pO₂ histograms) for normal cervix of nulliparous (top) and parous (bottom) women. N, number of patients; n, number of pO₂ measurements.

Pooled data for all cervical cancers of clinical stages FIGO I and II are presented in Fig. 2, top, whereas the respective pO₂ histogram for malignancies of stages FIGO III and IV are shown in Fig. 2, bottom. This compilation provides clear evidence that there are no statistically significant differences between the two groups (median pO₂ in FIGO I/II tumors, 14 mm Hg; median pO₂ in FIGO III/IV tumors, 11 mm Hg). This implies that the clinical stages of the cervical cancers investigated thus far cannot be the paramount factor determining tumor tissue oxygenation. Surprisingly, the number of pO₂ readings in the "hypoxic" class (0–2.5 mm Hg) is lower in FIGO III/IV than in FIGO I/II tumors.

Based on the oxygenation pattern of the malignancies investigated there is substantial experimental evidence that the occurrence of radiobiological hypoxia does not correlate with the

Table 2 Characteristics of healthy patients undergoing computerized pO₂ histography of the uterine cervix

	AK	BW	PF	JB	RM	FS	EG	UH	CH	NS	UM	NM	MM	KS
Age (yr)	29	27	35	50	42	83	44	23	23	22	29	23	26	41
Menopausal stage	Pre	Pre	Pre	Post	Pre	Post	Post	Pre	Pre	Pre	Pre	Pre	Pre	Pre
Parous status	p ^a	p	p	p	p	p	p	np	np	np	np	np	np	np
Mean pO ₂ (mm Hg)	13	24	11	8	25	41	22	59	11	48	81	40	26	59
Median pO ₂ (mm Hg)	4	18	4	7	18	39	14	53	7	46	84	34	19	57
10 percentile (mm Hg)	0	6	0	3	5	13	11	35	3	18	53	19	8	47
90 percentile (mm Hg)	38	43	32	13	64	64	47	89	24	86	108	69	55	74
pO ₂ readings between 0 and 2.5 mm Hg (%)	43	48	30	0	0	0	0	0	5	0	0	0	0	0

^a p, para; np, nullipara.

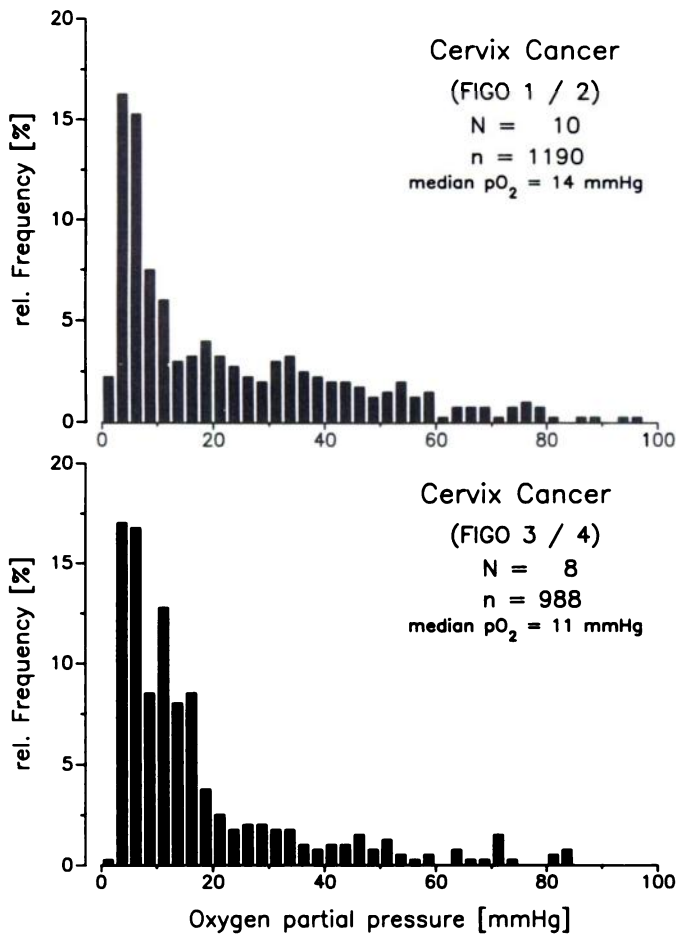


Fig. 2. pO₂ histograms derived from cervical cancers of different clinical stages (*top*, FIGO I/II; *bottom*, FIGO III/IV). *N*, number of patients; *n*, number of measured pO₂ values.

clinical stage and the histological grade and other clinically relevant parameters. Correlations between staging or grading and the number of pO₂ readings on zero level, the mean or median pO₂, and the 10% or 90% percentiles could not be detected.

There is marked tumor-to-tumor variability, even if tumors of the same clinical stage (FIGO II), grade (G2), and histology (squamous cell carcinomas) are compared (see Fig. 3). In the case presented in Fig. 3, *top*, all measured pO₂ values are higher than 18 mm Hg and thus indicative of a relative radiosensitivity >2.4 (17). In contrast, oxygenation of the cervical cancer shown in Fig. 3, *bottom*, contains a significant volume of tissue (at least 20%) with less than half-maximum radiosensitivity.

As a result of intratumor heterogeneities, a certain number of pO₂ measurements in different electrode tracks through a tumor is required in order to obtain sufficient information on the oxygenation status of an individual tumor. In 5 patients we compared the pO₂ histograms obtained from 2 "standard" electrode tracks (at 6 and 12 o'clock positions) with those evaluated from multiple tracks (up to 10 additional electrode passages). No significant differences were found when >40 pO₂ values were recorded per track. If the lowest pO₂ class (0–2.5 mm Hg) is considered, there were no differences when multiple *versus* "standard" electrode tracks were compared. Additionally, similar pO₂ histograms were usually obtained when the same tumor region was measured repeatedly during a 1-day observation period using different O₂-sensitive electrodes.

In the cervical cancers studied, high and low pO₂ values were randomly distributed in both tumor periphery and center.

DISCUSSION

Oxygen tension measurements were performed in the normal cervix and in cervical cancers of conscious women using a novel polarographic device capable of reliable tissue pO₂ determinations. In the normal cervix of nullipara, during controlled arterial blood gas status, a pO₂ distribution was found similar to that of most normal tissues (1, 17). In contrast, a left-shifted pO₂ histogram with a reduction of median oxygen levels and an asymmetry toward lower pO₂ values was observed in the cervix of para. The existence of tissue areas with less than half-maximum radiosensitivity (approximately 13% of the pO₂ readings) is a finding which has not been addressed previously and, in addition, had not been expected by earlier investigators. This pronounced left shift of the pO₂ histogram most probably is due to the scar formation in the cervix after vaginal delivery(ies). The biological and clinical significance of the lower oxygenation status of parous women is not clear at present and deserves further investigation.

When comparing the tissue oxygenation of cervical cancers (FIGO I-IV) with that found in the normal cervix of parous women, a clear-cut difference was not observed. In both instances, left-shifted pO₂ distributions were found with a higher percentage of pO₂ readings in lowest pO₂ class (0–2.5 mm Hg) in the normal cervix of parous women.

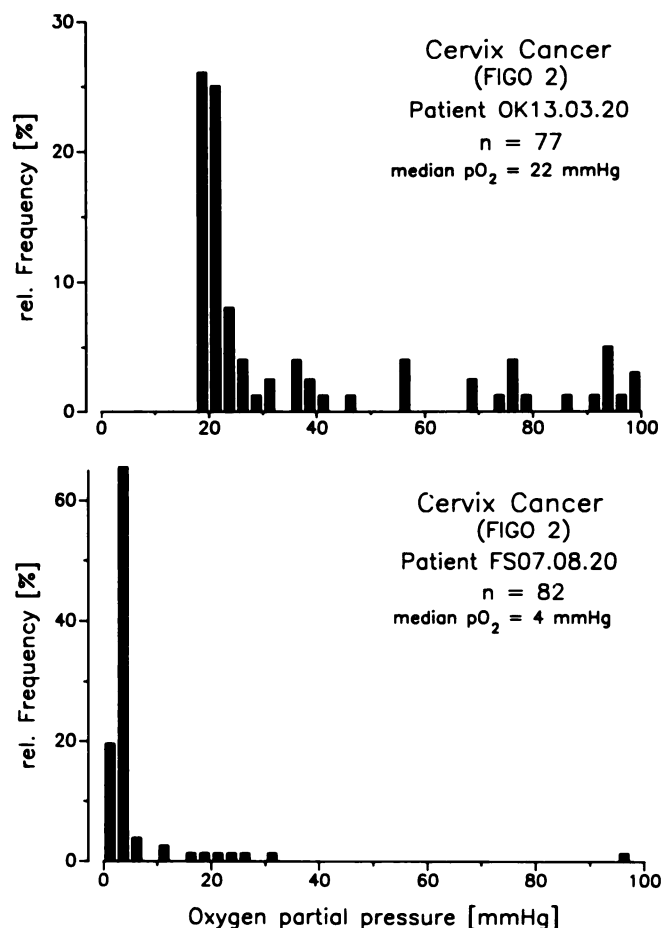


Fig. 3. pO₂ frequency distributions of two squamous cell carcinomas of the cervix (stage FIGO II, grade G2) substantiating marked tumor-to-tumor variability in the oxygenation status. *n*, number of pO₂ recordings.

Table 3 Tissue oxygen tension in the normal cervix and in cervical cancer of patients (n = number of patients)

Condition	pO ₂ (mm Hg)	n	Refs.
Normal cervix	41 (4-79) ^a	48	2, 3
Nullipara	48 ^b	7	This study
Para	13 ^b	7	This study
Cervix cancer			
Stage 0	26 ^a	33	2, 3
Stage I	17 ^a	16	2, 3
Stage II	19 ^a	19	2, 3
	14 ^b	9	This study
Stage III	12 ^b	7	This study

^a Estimated mean (range); measurement with bare electrodes in superficial tissue regions.

^b Median pO₂ value.

When stage II and III tumors are considered, almost identical median pO₂ values compared with the data evaluated for normal cervix of para were found (see Table 3). Only when the tumor data are related to the median pO₂ value of the normal cervix of nullipara is a ratio of approximately 3.4 for stage II tumors obtained. This latter ratio is distinctly higher than that reported earlier for stage II cervical cancers [2.2 (2) and 2.5 (10)]. This difference may partly be due to the fact that in the latter studies no distinction was made between nulliparous and parous patients.

As was the case with breast cancers (1), the oxygenation pattern and the occurrence of low pO₂ readings did not correlate with either the clinical stages and histological grades or with the tumor histology (squamous cell carcinomas *versus* adenocarcinomas), the location of the pO₂ measurements (center *versus* periphery), and a series of other clinically relevant factors. Again, from these clinical studies there is clear indication that the oxygenation status of individual tumors before therapy cannot be predicted solely on the basis of staging and/or grading. This is mostly due to pronounced tumor-to-tumor (and intratumor) pO₂ variabilities. Evaluation of the tissue oxygenation of individual tumors is thus mandatory to prove that tumor oxygenation can predict the overall prognosis and/or treatment outcome.

When comparing the oxygenation pattern of breast cancers (pathological stages T1-4) with that of cervical cancers (clinical stages FIGO I-IV), one striking difference has to be mentioned. Whereas the number of pO₂ readings in the lowest class is almost identical in the cervix and breast cancers investigated (2 *versus* 3%), the two pO₂ histograms are significantly different (*P* < 0.005), with a better oxygenation in the breast cancers (White test) (18, 19). This may be at least partially due to the larger size of the cervical cancers investigated (mean maximum diameter in cervical cancers, 6.1 cm *versus* 3.1 cm in breast cancers; *P* < 0.0001). However, when the cervix and breast

cancers are considered as separate groups there is thus far no indication that a correlation exists between median pO₂ values and tumor sizes.

ACKNOWLEDGMENTS

We wish to thank Dr. Debra Bickes-Kelleher for her helpful suggestions in preparing the manuscript and Anne Deutschmann-Fleck for secretarial assistance.

REFERENCES

- Vaupel, P., Schlenger, K., Knoop, C., and Höckel, M. Oxygenation of human tumors: evaluation of tissue oxygen distribution in breast cancers by computerized O₂ tension measurements. *Cancer Res.*, 51: 3316-3322, 1991.
- Kolstad, P. *Vascularization, Oxygen Tension, and Radiocurability in Cancer of the Cervix*. Oslo: Universitetsforlaget, 1964.
- Kolstad, P. Inter-capillary distance, oxygen tension and local recurrence in cervix cancer. *Scand. J. Clin. Lab. Invest. Suppl.*, 106: 145-157, 1968.
- Awwad, H. K., Naggar, M. E., Mocktar, N., and Barsoum, M. Inter-capillary distance measurement as an indicator of hypoxia in carcinoma of the cervix uteri. *Int. J. Radiat. Oncol. Biol. Phys.*, 12: 1329-1333, 1986.
- Révész, L., Siracká, E., Siracký, J., Delides, G., and Pavlaki, K. Variation of vascular density within and between tumors of the uterine cervix and its predictive value for radiotherapy. *Int. J. Radiat. Oncol. Biol. Phys.*, 16: 1161-1163, 1989.
- Siracká, E., Révész, L., Kováč, R., and Siracký, J. Vascular density in carcinoma of the uterine cervix and its predictive value for radiotherapy. *Int. J. Cancer*, 41: 819-822, 1988.
- Siracký, J., Siracká, E., Pappová, N., and Révész, L. Vascularization and radiocurability in cancer of the uterine cervix. A retrospective study. *Neoplasma (Bratisl.)*, 29: 183-188, 1982.
- Siracký, J., Siracká, E., Kováč, R., and Révész, L. Prognostic significance of vascular density and a malignancy grading in radiation treated uterine cervix carcinoma. *Neoplasma (Bratisl.)*, 35: 289-296, 1988.
- Bergsjö, P., Christensen, O. J., and Kolstad, P. Oxygen tension in cancer of the cervix following administration of vasodilator drugs during oxygen inhalation. *Cancer (Phila.)*, 20: 1625-1634, 1967.
- Bergsjö, P., and Evans, J. C. Tissue oxygen tension of cervix cancer. Comparison of effects of breathing a carbon dioxide mixture and pure oxygen. *Acta Radiol. Ther. Phys. Biol.*, 7: 1-11, 1968.
- Bergsjö, P., and Evans, J. C. Oxygen tension of cervical carcinoma during the early phase of external irradiation. I. Measurements with a Clark micro electrode. *Scand. J. Clin. Lab. Invest.*, 22: 156-166, 1968.
- Bergsjö, P., and Evans, J. C. Oxygen tension of cervical carcinoma during the early phase of external irradiation. II. Measurements with bare platinum micro electrodes. *Scand. J. Clin. Lab. Invest.*, 27: 71-82, 1971.
- Hutten, H., Meiners, K., and Zander, R. A method for the polarographic measurement of oxygen solubility coefficients in hydrous solutions of electrolytes. *Biomed. Techn.*, 27: 7-13, 1982.
- Zander, R. Cellular oxygen concentration. *Adv. Exp. Med. Biol.*, 75: 463-467, 1976.
- International Union Against Cancer. *TMN Classification of Malignant Tumours*, Ed. 4. Berlin: Springer-Verlag, 1987.
- Fu, Y. S., and Reagan, J. W. *Pathology of the Uterine Cervix, Vagina, and Vulva*. Philadelphia: W. B. Saunders Co., 1989.
- Vaupel, P., Kallinowski, F., and Okunieff, P. Blood flow, oxygen and nutrient supply, and metabolic microenvironment of human tumors: a review. *Cancer Res.*, 49: 6449-6465, 1989.
- White, C. The use of ranks in a test of significance for comparing two treatments. *Biometrics*, 8: 33-41, 1952.
- Raatz, U. Eine Modifikation des White-Tests bei grossen Stichproben. *Biometr. Zeitschr.*, 8: 42-54, 1966.