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Oxygenation of Carcinomas of the Uterine Cervix: Evaluation by Computerized O_2 Tension Measurements

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ABSTRACT

Direct oxygen partial pressure (pO_2) readings in cancers of the cervix and in the normal cervix of nulliparous or parous women were obtained using a computerized pO_2 histography system. The oxygenation status of the tumors was evaluated as a function of clinical staging and histological grading. pO_2 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, pO_2 measurements in the normal cervix of nulliparous women resulted in oxygenation patterns which were characteristic for normal, adequately supplied tissues (median pO_2, 48 mm Hg) with approximately 1% of the pO_2 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) pO_2 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 pO_2 value was 13 mm Hg (with approximately 14% of the pO_2 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 pO_2 class), and 11 mm Hg in International Federation of Gynecologists and Obstetricians III/IV cancers (1% of the pO_2 data in the lowest class). To date, 5 of 18 cervical cancers exhibited pO_2 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, pO_2 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 O_2 concentrations instead of O_2 partial pressures (O_2 tensions). For the evaluation of oxygen tension (pO_2) distribution in tissues, membrane-covered O_2 sensors are required (13). A direct conversion of O_2 concentrations (cO_2) into pO_2 values according to the Henry-Dalton law ($cO_2 = \alpha \cdot pO_2$) is not possible, since the O_2 solubility coefficient (α) is anisotropic in tissues (14). In addition, the validity of the O_2 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 pO_2 readings in normal and malignant tissues are now possible using a novel, commercially available technique (computerized pO_2 histography) which allows for the systematic evaluation of the tissue oxygenation status. The measuring procedure uses a computerized O_2 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 pO_2 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 pO_2 data obtained with this method match with earlier results suggesting low mean O_2 tensions or concentrations in cervical cancers? What are the absolute pO_2 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 pO_2 distribution in the normal cervix of para *versus* nullipara, and the evaluation of O_2 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 pO_2 measurements in individual tumors for local control after therapy, we have evaluated intratumor pO_2 measurements in 7 pre- and 11 postmenopausal conscious patients (age, 27–80 years) entering the study. Fifteen women presented with histologically confirmed squamous cell

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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 FIGO[2] 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 hysterography 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 vaginosonography. 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 cervices 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 position[3]). 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

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

MR14.12.52 TR26.02.42 RB05.02.63 SS13.06.48 HT29.09.33 FS07.08.20 OK13.03.20 MT05.04.13 LS23.08.11 EW03.09.09 RH07.02.57 BM19.09.55 IB31.10.40 GL24.02.38 DB22.10.35 GW12.04.22 HD23.10.20 MW26.05.21

Age (yr)	37	47	27	41	56	69	69	76	78	80	33	34	49	52	54	67	69	68
Clinical staging (FIGO)	Ib	IIa	IIb	IIb	IIb	IIb	IIb	IIb	IIb	IIb	IIIb	IIIb	IIIb	IIIb	IIIb	IIIb	IIIb	IVa
Histology	s.c.c.[a]	s.c.c.	s.c.c.	s.c.c.	s.c.c.	s.c.c.	s.c.c.	ad.ca.	s.c.c.	s.c.c.	s.c.c.	ad.ca	s.c.c.	s.c.c.	s.c.c.	s.c.c.	s.c.c.	s.c.c.	ad.ca.
Histopathological grading	G2	G2	G3	n.d.	n.d.	G2	G2	G2	G1	G2	G2	G1	G2	G2	G2	G2	G2	G2	G1
Maximum tumor diameter (cm)	2.0	5.0	5.0	6.0	5.5	6.0	>6.0	3.0	5.5	5.5	>6.0	10.0	8.0	7.0	6.0	8.0	3.0	10.0	
Menopausal stage	Pre	Pre	Pre	Pre	Post	Post	Post	Post	Post	Post	Pre	Pre	Pre	Post	Post	Post	Post	Post	Post
Karnofsky index (%)	100	100	100	100	100	90	100	100	90	80	100	100	80	90	90	90	100	100	
BP (mm Hg)	140/90	130/90	120/80	140/85	140/85	180/90	150/90	170/105	160/95	140/70	105/70	130/85	135/90	150/105	140/90	120/70	130/80	150/85	
Heart rate (min^{-1})	91	88	87	90	75	72	72	97	90	64	102	68	100	94	102	80	64	60	
Hemoglobin concentration (g/liter)	128	135	127	151	152	121	99	142	102	129	136	n.d.	n.d.	95	95	102	151	148	
HbO_2 saturation (sat. %)	98	100	100	97	98	98	99	97	96	97	98	97	98	95	97	98	98	99	
Mean pO_2 (mm Hg)	26	17	22	31	21	13	38	28	29	20	16	19	11	12	34	18	18	6	
Median pO_2 (mm Hg)	14	10	16	26	14	4	22	29	11	5	11	14	6	4	12	14	8	5	
10 percentile (mm Hg)	9	5	3	8	4	2	18	6	6	3	6	6	3	3	10	9	3	3	
90 percentile (mm Hg)	56	43	50	75	51	39	90	58	75	63	33	45	28	37	81	37	51	10	
pO_2 readings between 0 and 2.5 mm Hg (%)	0	0	6	0	0	13	0	0	0	3	0	0	0	7	0	0	0	1	

[a] BP, arterial blood pressure; HbO_2, arterial oxyhemoglobin saturation; s.c.c., squamous cell carcinoma; ad.ca., adenocarcinoma; n.d., not determined.

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

[3] Unpublished results.

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 O_2-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 pO_2 readings ($n > 50$) were obtained in order to present the data by means of pO_2 frequency distributions (pO_2 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 pO_2 probe was automatically removed from the tissue. In cancer patients the pO_2 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 pO_2 measurements were exclusively performed during arterial normoxemia, basic cardiovascular parameters (*e.g.*, heart rate, arterial blood pressure) and factors determining the arterial O_2 concentration (*e.g.*, hemoglobin concentration, hematocrit, arterial oxyhemoglobin saturation) were monitored during the measuring procedures (1).

Statistical Analysis. Using an on-line computing system, pO_2 histograms (*i.e.*, pO_2 frequency distributions) were obtained with a class width of 2.5 mm Hg. The distribution of the measured pO_2 values was characterized by the mean pO_2, the median pO_2, 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 pO_2 histography system, pO_2 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) pO_2 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 pO_2 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 pO_2 histograms in cancer patients were similar to those obtained in the normal cervix of parous women. Thus far, 5 of 18 cervical cancers exhibited pO_2 values between zero and 2.5 mm Hg, *i.e.*, tissue areas with less than half-maximum radiosensitivity. One of 7 normal cervices in nulliparas and 3 of 7 cervices in paras exhibited pO_2 values between zero and 2.5 mm Hg.

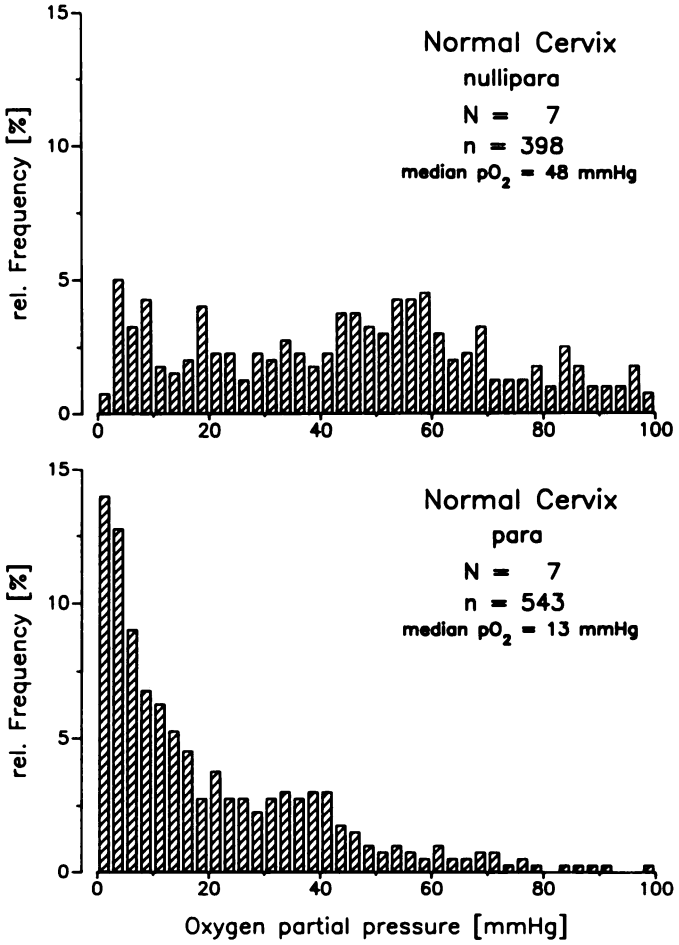

Fig. 1. Frequency distributions of measured oxygen partial pressures (pO_2 histograms) for normal cervix of nulliparous (*top*) and parous (*bottom*) women. *N*, number of patients; *n*, number of pO_2 measurements.

Pooled data for all cervical cancers of clinical stages FIGO I and II are presented in Fig. 2, *top*, whereas the respective pO_2 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 pO_2 in FIGO I/II tumors, 14 mm Hg; median pO_2 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 pO_2 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 pO_2 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.

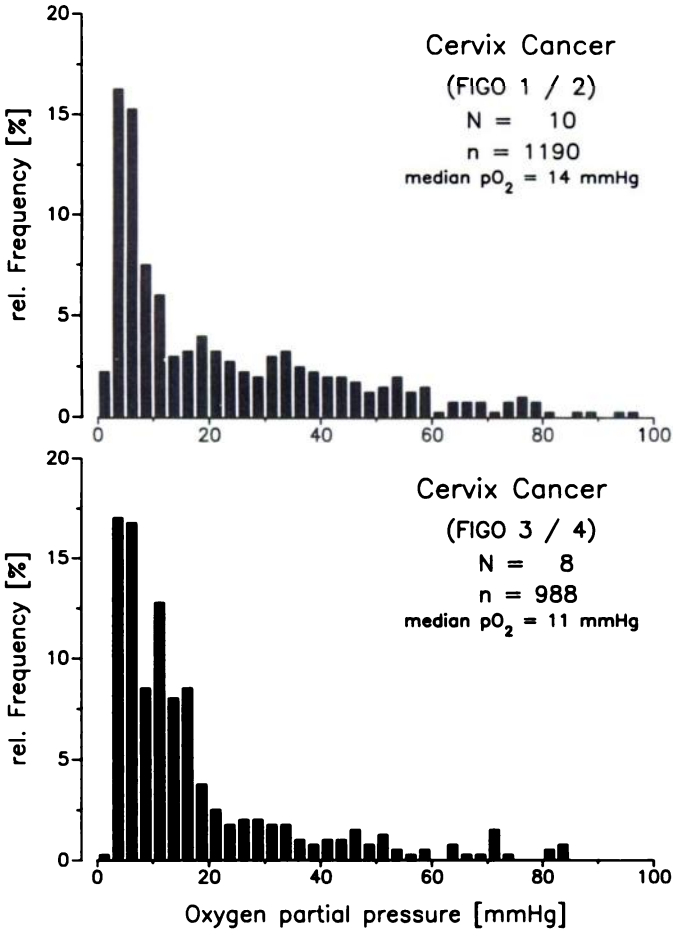

Fig. 2. pO_2 histograms derived from cervical cancers of different clinical stages (*top*, FIGO I/II; *bottom*, FIGO III/IV). *N*, number of patients; *n*, number of measured pO_2 values.

clinical stage and the histological grade and other clinically relevant parameters. Correlations between staging or grading and the number of pO_2 readings on zero level, the mean or median pO_2, 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 pO_2 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 pO_2 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 pO_2 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 pO_2 values were recorded per track. If the lowest pO_2 class (0–2.5 mm Hg) is considered, there were no differences when multiple *versus* "standard" electrode tracks were compared. Additionally, similar pO_2 histograms were usually obtained when the same tumor region was measured repeatedly during a 1-day observation period using different O_2-sensitive electrodes.

In the cervical cancers studied, high and low pO_2 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 pO_2 determinations. In the normal cervix of nullipara, during controlled arterial blood gas status, a pO_2 distribution was found similar to that of most normal tissues (1, 17). In contrast, a left-shifted pO_2 histogram with a reduction of median oxygen levels and an asymmetry toward lower pO_2 values was observed in the cervix of para. The existence of tissue areas with less than half-maximum radiosensitivity (approximately 13% of the pO_2 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 pO_2 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 pO_2 distributions were found with a higher percentage of pO_2 readings in lowest pO_2 class (0–2.5 mm Hg) in the normal cervix of parous women.

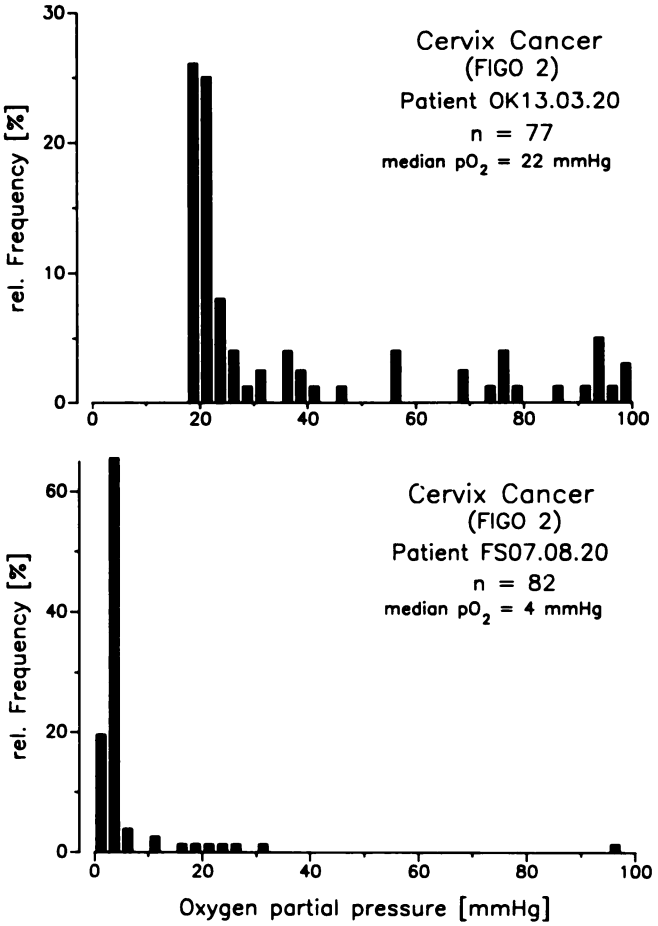

Fig. 3. pO_2 frequency distributions of two squamous cell carcinomas of the cervix (stage FIGO II, grade G2) substantiating marked tumor-to-tumor variability in the oxygenation status. *n*, number of pO_2 recordings.

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 pO_2 value.

When stage II and III tumors are considered, almost identical median pO_2 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 pO_2 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 pO_2 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 pO_2 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) pO_2 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 pO_2 readings in the lowest class is almost identical in the cervix and breast cancers investigated (2 *versus* 3%), the two pO_2 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 pO_2 values and tumor sizes.

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