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Forum Review

Detection and Characterization of Tumor Hypoxia Using pO_2 Histography

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ABSTRACT

Data from 125 studies describing the pretreatment oxygenation status as measured in the clinical setting using the computerized Eppendorf pO_2 histography system have been compiled in this article. Tumor oxygenation is heterogeneous and severely compromised as compared to normal tissue. Hypoxia results from inadequate perfusion and diffusion within tumors and from a reduced O_2 transport capacity in anemic patients. The development of tumor hypoxia is independent of a series of relevant tumor characteristics (*e.g.*, clinical size, stage, histology, and grade) and various patient demographics. Overall median pO_2 in cancers of the uterine cervix, head and neck, and breast is 10 mm Hg with the overall hypoxic fraction ($pO_2 \leq 2.5$ mm Hg) being approx. 25%. Metastatic lesions do not substantially deviate from the oxygenation status of (their) primary tumors. Whereas normal tissue oxygenation is independent of the hemoglobin level over the range of 8–15 g/dL, hypoxia is more pronounced in anemic patients and above this range in some cancers. Identification of tumor hypoxia may allow an assessment of a tumor's potential to develop an aggressive phenotype or acquired treatment resistance, both of which lead to poor prognosis. Detection of hypoxia in the clinical setting may therefore be helpful in selecting high-risk patients for individual and/or more intensive treatment schedules. *Antioxid. Redox Signal.* 9, 1221–1235.

INTRODUCTION

For many years, the identification of tumor hypoxia, its systematic characterization, and the assessment of its clinical relevance were not possible due to the lack of methods suitable for the routine measurement of intratumoral oxygen tensions in patients. In the late 1980s, a novel and clinically applicable standardized procedure was established enabling the "routine" determination of tumor oxygenation in accessible primary tumors, local recurrences, and metastatic lesions in patients using a computerized polarographic needle electrode system (57, 64, 143). Within a relatively short period of time, the significance of tumor oxygenation for therapy outcome and malignant progression became evident in numerous experimental and clinical studies.

In this article, current knowledge concerning the oxygenation status of tumors and the occurrence of hypoxia in solid malignancies have been compiled and the mechanisms causing tumor hypoxia are discussed. All data presented here are derived from clinical studies on the *pretreatment* oxygenation status of solid tumors using the computerized Eppendorf pO_2 histography system. This technique, based on mechanically stable O_2 microsensors, is minimally invasive and allows the direct and reliable measurement of oxygen partial pressures (pO_2 values) in tissues. It provides quantitative measures and is (still) regarded as the "gold standard" for the assessment of the tissue oxygenation status (114).

DEFINITION OF HYPOXIA

In pathophysiological terms, hypoxia is defined as a state of reduced O_2 availability or decreased O_2 partial pressures (O_2

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tensions, pO_2 values) below critical thresholds, thus resulting in limitations of characteristic cellular or organ functions. In contrast to normal tissues, malignant tumors obviously have no "physiological" functions. Thus, tumor hypoxia cannot be defined by functional deficits, although areas of necrosis—which are often found in tumors on microscopic examination—indicate the loss of vital cellular functions. In the following, the term hypoxia is used to describe critical O_2 levels below which clinical, biological, and/or molecular effects are progressively observed (*e.g.*, acquired treatment resistance, ATP depletion, binding of hypoxic markers, slowing of proliferation rate, proteome and genome changes, metabolic hypoxic stress response, and development of an aggressive phenotype). In this discussion of hypoxic thresholds, it is important to note that, for any particular functional parameter, a sharp threshold between "hypoxia" (*i.e.*, more hypoxic tumors) and "normoxia" (*i.e.*, less hypoxic tumors) does not exist and should not be expected (51). In this article, four descriptors of the tumor oxygenation status are used: the median tumor pO_2 value, the fraction of pO_2 values $\leq$2.5 mm Hg (HF 2.5), the fraction of pO_2 values $\leq$5 mm Hg (HF 5), and the fraction of pO_2 values $\leq$10 mm Hg (HF 10).

Unfortunately, in an increasing number of reports on tumor oxygenation, the term hypoxia has been used in a somewhat unprecise manner, without providing clear definitions for the (experimental) conditions used and scientific questions being asked. As a result, discussions involving researchers and clinicians have often led to confusion since the single term hypoxia has been used by many groups to describe quite different conditions (51).

Anoxia describes the (patho-)physiological state, where no O_2 is detected in the tissue ($pO_2 = 0$ mm Hg).

PATHOGENESIS OF TUMOR HYPOXIA

Using the Eppendorf pO_2 histography system (Eppendorf, Hamburg, Germany), our investigations, carried out between 1987 and 2005, demonstrated that the presence of hypoxic tissue areas (*e.g.*, areas with pO_2 values $\leq$2.5 mm Hg) is a characteristic pathophysiological property of locally advanced solid tumors, and such areas have been found in a wide range of human malignancies.

Evidence has accumulated showing that at least 50–60% of locally advanced solid tumors may exhibit hypoxic and/or anoxic tissue areas that are heterogeneously distributed within the tumor mass. The hypoxic (or anoxic) areas arise as a result of an imbalance between the supply and consumption of oxygen. Whereas in normal tissues or organs the O_2 supply is matched to the metabolic requirements, in solid tumors the O_2 consumption rate of neoplastic as well as stromal cells may exceed the compromised oxygen availability and may result in the development of tissue areas with very low O_2 levels.

Tumor hypoxia predominantly results from an inadequate perfusion due to severe structural and functional abnormalities of the tumor microcirculation (for reviews, see Refs. 124, 125, 129, 139). Hypoxic (micro-)regions are heterogeneously distributed within the tumor mass and may be located adjacent to regions with O_2 tensions in the range of those found in the normal tissue neighboring the neoplastic lesion. *Perfusion-limited O_2 delivery* leads to *ischemic hypoxia*, which is often transient. For this reason, this type of hypoxia is also called "acute" hypoxia, a term that does not take into account the mechanisms underlying this condition (135, 146).

Hypoxia in tumors can also be caused by an *increase in diffusion distances*, so that cells far away ($>$70 μm) from the nutritive blood vessel receive less oxygen than required. This condition is termed *diffusion-limited hypoxia*, also known as "chronic" hypoxia. In addition to enlarged diffusion distances, an *adverse diffusion geometry* (*e.g.*, concurrent *vs.* countercurrent tumor microvessels) can also cause hypoxia (130).

Tumor-associated or *therapy-induced anemia* can lead to a reduced O_2 transport capacity of the blood, a major factor contributing to the development of hypoxia (*anemic hypoxia*). This type of hypoxia is especially pronounced in tumors or tumor areas exhibiting low perfusion rates. A similar condition can be caused by carboxyhemoglobin (HbCO) formation in heavy smokers, which leads to a functional anemia, since hemoglobin blocked by carbon monoxide (CO) is no longer capable of transporting oxygen.

Very often, tumor microvessels are perfused (at least transiently) by plasma only. In this situation, *hypoxemic hypoxia* develops very rapidly around these vessels because only a few tumor cells at the arterial end can be supplied adequately. Similarly, hypoxia can rapidly develop in (primary or metastatic) liver tumors that are preferentially supplied by branches of the portal vein. There is abundant evidence for the existence of a substantial heterogeneity in the development and extent of tumor hypoxia due to pronounced intratumor (and intertumor) variabilities in vascularity and perfusion rates (for reviews, see Refs. 125, 128, 139).

THE COMPUTERIZED pO_2 HISTOGRAPHY SYSTEM

Over the past 15 years, the oxygenation status of solid tumors has been evaluated by investigators in many specialized centers. Assessment of the tumor oxygenation status by invasive and noninvasive procedures have been reviewed repeatedly (33, 42, 48, 51, 86, 114, 121, 146). Many methods can directly or indirectly detect tumor hypoxia. The choice of method for a particular experimental or clinical need should take into account the feasibility of the approaches available in terms of invasiveness, level of resolution required, whether measurements of a direct or indirect parameter are necessary, and of course financial considerations.

The present "gold standard" is still the intratumor polarographic measurement of pO_2 values using the microsensor technique that adheres to the systematic random sampling principle (57, 143). Up until now it has been the most commonly used method in the clinical setting with $\geq$125 research articles having been published so far (Fig. 1). However, no single method will probably be suitable for all situations, and where possible, use of more than one technique may be advisable. In all instances, careful interpretation of the data obtained by an experienced investigator is paramount, and researchers should bear in mind the exact parameters measured and consider the limi-

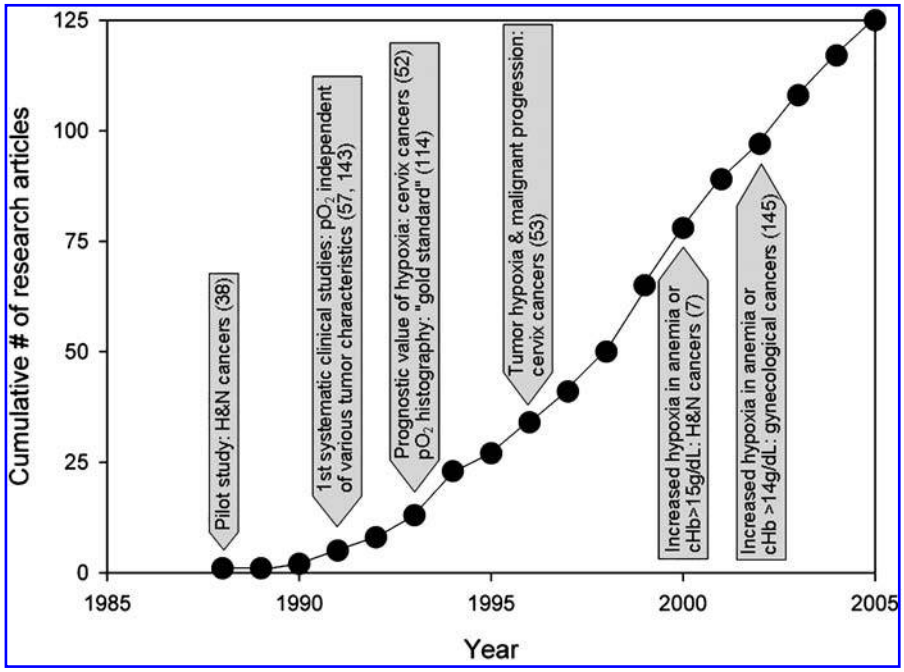

FIG. 1. Cumulative number of research articles providing quantitative data on the pretreatment oxygenation status of solid tumors assessed using pO_2 histography between 1988 and 2005. Milestones in the field of tumor oxygenation measurement are shown by the *shaded arrows.*

tations of the specific method used (Table 1). Since hypoxia has been repeatedly and convincingly identified as a major independent and adverse prognostic factor for tumor progression and for resistance to anticancer treatment, currently available techniques have to be standardized for hypoxia assessment and quantification to provide independent prognostic information for optimization and individualization of cancer patient treatment.

The pO_2 readings and data presented in this article were all measured pretherapeutically, adhering to a standard procedure. The technique has been described in detail previously (57, 143). Briefly, a 250–350 μm diameter O_2-sensitive polarographic needle electrode (housing a membrane-covered recessed gold microcathode in the form of a gold wire 12 or 17 μm in diameter) is inserted into the tumor following calibration of the probes. A computer-controlled stepping motor then advances the electrode 1 mm into the tissue, after which the needle is retracted 0.3 mm to minimize compression artifacts, which would

TABLE 1. CRITICAL EVALUATION OF THE COMPUTERIZED pO_2 HISTOGRAPHY SYSTEM

Advantages	*Disadvantages*
• Measures absolute pO_2 values ($\pm$ 1 mm Hg SD) • Provides pO_2 distribution within a tissue microarea • Sufficient spatial resolution (~100–500 cells) • Rapid application • Rapid data sampling • Very rapid electrode response • Provides real-time measurements • Can provide 3D-pO_2 distribution with multiple sampling • Allows classification based on biologically or therapeutically relevant hypoxic fractions • Fraction of pO_2 readings <0 mm Hg enables assessment of the quality of measurement • Safe diagnostic tool • Provides several quantitative descriptive parameters of the pO_2 histogram (= pO_2 distribution curve) • Provides pO_2 profiles within a tumor • Detection of hypoxia by this method has prognostic potential • 20–25 pO_2 measurements sufficient to categorize tumors as hypoxic or normoxic (28) 5 $\times$ 20 pO_2 measurements is optimal for assessment of tumor oxygenation status (150)	• (Minimally) invasive • Needs experienced investigator • Single time point measurement • Temporal assessment at a single location not possible • Restricted to accessible tumors • No coverage of the entire tumor volume (*i.e.,* hypoxia cannot be excluded distant from electrode tracks) • Cannot differentiate between tumor and normal tissues, or between viable and necrotic regions (unless needle core biopsies of the electrode tracks are taken and/or probe location is monitored by MRI, CT or ultrasound) • Limited applicability for sequential pO_2 readings • Minimum number of measurements within several electrode tracks necessary to describe a "true" pO_2 distribution • Cannot differentiate between vascular, interstitial and intracellular compartment • May not be used during halothane anesthesia • Pronounced inter-institutional differences for the same tumor entity

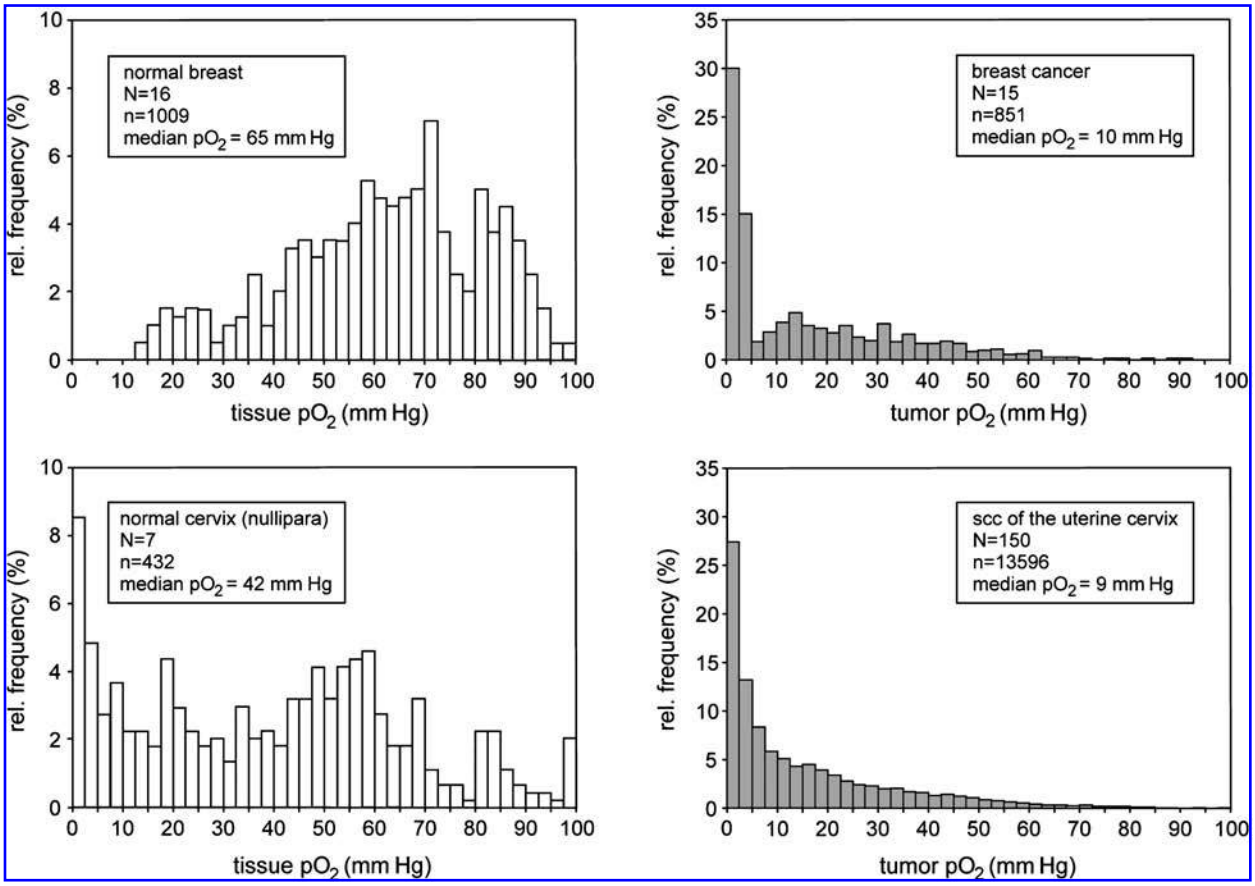

FIG. 2. Frequency distribution (histograms) of oxygen partial pressures (pO_2) measured in normal breast (*upper left panel*) and in locally advanced breast cancers (T1b–T4, *upper right panel*), in normal cervix of nullipara (*lower left panel*), and in squamous cell carcinomas (SCC) of the uterine cervix (*lower right panel*). N = number of patients; n = number of pO_2 values measured.

otherwise occur on the membrane of the sensor. This movement pattern leads to an effective forward step length of 0.7 mm. The local pO_2 is measured 1.4 sec after the backward motion. Single local pO_2 measurements are performed in <40 msec. The overall length of the electrode tracks and the number of measurement tracks depends on the size of the individual tumor investigated (57, 143). After pO_2 measurements in the tissue, recalibration of the O_2 sensor is mandatory. So far, no adverse side effects of this technique have been reported (*e.g.*, major bleeding, infection, or increased metastatic spread) that might limit its clinical application.

In our institution, for validation of the standard procedure, a series of pO_2 measurements were performed in the same (conscious) patients (a) at two different times prior to treatment, (b) with two different histographs, and (c) by two different investigators. In another series, in addition to the measurements within two electrode tracks, up to eight further measurements at different sites were carried out in the same tumor. If the standard two-track procedure was performed, the interobserver variation of the median pO_2 with respect to histograph, operator, and time of measurement was of the magnitude of only 2–3 mm Hg. Intratumoral variation between measuring positions located just a few millimeters away from each other was of the same order as the variation between measuring positions, which were some centimeters apart. However, although intratumoral heterogeneity in microregional pO_2 values was pronounced, intertumoral heterogeneity was significantly higher, thus allowing the use of the median pO_2 as determined with the standard procedure for characterization of individual cervical cancers (55).

Before pO_2 measurements along linear tracks in cancer tissues were performed in conscious patients, pO_2 readings were routinely obtained in subcutaneous tissues. As a further routine procedure for cervix cancers in our institution, core biopsies of ~2 mm in diameter and 20 mm in length were taken from those tumor areas where the pO_2 determinations had been made and subsequently processed for histology (53).

In our institution, monitoring of relevant systemic parameters which critically influence tissue oxygenation (cHb, hematocrit, arterial oxyhemoglobin saturation, heart rate, and arterial blood pressure) was mandatory.

OXYGENATION STATUS OF CARCINOMAS OF THE UTERINE CERVIX

Current knowledge on the oxygenation status of primary cancers of the uterine cervix generally refers to pretherapeutic data obtained in pre- and postmenopausal, conscious women, re-

Table 2. Pretherapeutic Oxygenation Status of Primary, Locally Advanced Cancer of the Uterine Cervix and Prognostic Significance of Tumor Hypoxia (n = Number of Patients)

Center	n	*Median pO_2 (mm Hg) [range]*	*HF 2.5 (%)*	*HF 5 (%)*	*HF 10 (%)*	*Prognostic significance of tumor hypoxia*		*References*
						Endpoint	*Oxygenation parameter*	
Mainz/Leipzig	150	10 [2–34]	23	37	50	DFS, OS	$pO_2 < 10$ mm Hg	52, 53, 58, 59
Toronto	135	5 [0–94]		50		DFS, PFS, DS[a]	$pO_2 < 5$ mm Hg	28, 40, 41, 85, 102, 150
Halle	87	17 [0–81]	16	26				29, 30, 47
Leipzig	86	5 [1–57]						78
Vienna	51	10 [0–60]	22	28	50	DFS, (LC)	$pO_2 < 10$ mm Hg	67
Oslo	49	4 [1–25]	47	64	76	DFS, OS, LC	HSV[b]	81, 82, 106, 117, 118,
						DS	$pO_2 < 5$ mm Hg	119, 120
							$pO_2 < 10$ mm Hg	
Manchester	43	3 [0–42]	39	58	75			2, 21, 99
	30	6 [0–41]						20
Paris	37	12	15	17	21			71, 73, 75
Aarhus	24	3 [0–19]	49	61	73			99
Vancouver	19	3 [0–34]	38	66	76			3, 99
Vienna	10	17 [3–54]		42				148
Durham	9	5		61				13
Overall	730	9	28	44	59			

[a]In node-negative patients.

[b]Hypoxic subvolume calculated as the product of the total tumor volume and the relative frequency of hypoxic pO_2 readings <5 mm Hg.

There may be some overlap in patients reported from the same institution.

Empty boxes indicate lack of suitable information.

ferred to the Departments of Gynecology and Obstetrics in Mainz (1989–1998) and Leipzig (1998–2005). Mean and median O_2 tensions obtained from >13,500 measurements in 150 primary carcinomas of the uterine cervix were, on average, distinctly lower than in normal tissues (Fig. 2). Oxygen tensions measured in the normal cervix of nulliparous women revealed a median pO_2 of 42 mm Hg, whereas in locally advanced cancers of the cervix (stages FIGO Ib-IVa), the median pO_2 was 10 mm Hg (Table 2). When tumors of different clinical sizes are compared, there is no evidence of a correlation between the maximum tumor diameter and the median pO_2, the fraction of pO_2 values $\leq$2.5 mm Hg or the fraction of pO_2 values $\leq$5 mm Hg. In addition, there is no characteristic topological distribution of O_2 tensions within cervix cancers (*i.e.*, as a function of the measurement site; *e.g.*, tumor periphery *vs.* tumor center).

The oxygenation status and the extent of pretherapeutically measured hypoxic tissue areas are independent of the FIGO stage, histological type, and pathohistological grade. Similarly, there was no association between the oxygenation patterns and parity, menopausal status, smoking habits, or a series of other clinically relevant parameters. In cervical cancers, the median pO_2 values rose with increasing hemoglobin concentrations over the range from 10 to 13 g/dL. At Hb levels >14 g/dL, a worsening of the tumor oxygenation became apparent (135,140, 145).

About 60% of locally advanced carcinomas of the uterine cervix (FIGO stages Ib-III) exhibited hypoxic ($pO_2 \leq 2.5$ mm Hg) and/or anoxic ($pO_2 = 0$ mm Hg) tissue areas, which were heterogeneously distributed within the tumor mass.

From our systematic studies on the oxygenation status of locally advanced solid tumors, there was clear evidence that tumor-to-tumor variability in the oxygenation status was significantly greater than intratumor variability, both for squamous cell carcinomas and for adenocarcinomas of the uterine cervix (50, 51, 54).

To clarify whether the *pathological tumor stage* (pT), rather than the FIGO stage may have an impact on the oxygenation status, pathological tumor staging was performed based on histopathological investigation of the surgical specimens following radical hysterectomy or exenteration and lymph node dissection in a subgroup of 65 patients treated with primary surgery (with curative intent). This procedure identified a median maximum (histological) tumor diameter of 40 mm (49, 50). In tumors with a maximum extension <40 mm ($n = 37$), the median pO_2 was 11 mm Hg, which was significantly higher than the respective pO_2 value in tumors with a maximum diameter >40 mm ($n = 28$, median $pO_2 = 5$ mm Hg; $p < 0.05$). Median pO_2 values in stage pT1b tumors were significantly higher (18 mm Hg) than in pT2b lesions (5 mm Hg, $p < 0.05$). Hypoxic fractions were slightly lower in pT1b (bulky) tumors than in pT2b malignancies. From these data it can be concluded that only a detailed histopathological tumor staging using surgical specimens enables detection of stage- and size-related differences in the oxygenation status of primary cancers of the uterine cervix. Clinical tumor dimensions and FIGO staging are not sufficiently accurate to allow for the estimation and characterization of the tumor oxygenation (50).

In an earlier study, Sundfør *et al*. (117) pointed out that *adenocarcinomas* (AC) of the uterine cervix were significantly better oxygenated than squamous cell carcinomas (SCC). In our studies, however, pO_2 values were comparable in tumors of both histologies: median $pO_2 = 11$ mm Hg in SCC *versus* 12

mm Hg in AC, and mean pO_2 = 16 mm Hg in SCC *versus* 18 mm Hg in AC. There were only slight differences in the fraction of pO_2 values ≤2.5 mm Hg (25% in SCC *vs.* 16% in AC), in the fraction of pO_2 values ≤5 mm Hg (38% in SCC *vs.* 32% in AC) and in the percentage of patients with tumor pO_2 values ≤2.5 mm Hg (60% in SCC *vs.* 66% in AC). The better stage-for-stage prognosis for SCC than for AC of the uterine cervix thus cannot be explained by a substantially different oxygenation status between tumors with these histologies.

Measurements of intratumoral oxygenation in pelvic relapses of cervical carcinomas with a similar methodological approach as developed for the primary disease showed a pronounced shift to more hypoxic oxygenation profiles in the recurrent tumors as compared to the primary lesions (56). Median pO_2 values in 46 pelvic recurrences of SCC were significantly lower than the median pO_2 values of 95 primary tumors of comparable sizes (4 *vs.* 11 mm Hg, $p < 0.001$).

In *locally recurrent tumors*, no significant differences in the oxygenation status between SCC and AC were observed. For both histologies the median pO_2 was lower, and the hypoxic fraction with pO_2 values ≤2.5 mm Hg was higher in recurrent tumors than in the primaries. The percentage of patients with pO_2 values ≤2.5 mm Hg in recurrent tumors was 77% for SCC (n = 46) and 87% for AC (n = 14), respectively.

An analysis of intergroup differences in tumor oxygenation indicated that the greater the extent of hypoxia in primary tumors, the higher the probability of local recurrence of cervix cancers.

When the available data on pretreatment tumor oxygenation of locally advanced cancers of the uterine cervix are summarized (50, 56, 57, 133), there is evidence that

- Oxygenation in tumors is heterogeneous and compromised as compared to normal tissues.
- Tumor oxygenation is not regulated according to the metabolic demand as is the case in normal tissues.
- Causative factors for the development of hypoxia are limitations in perfusion and diffusion as well as tumor-associated anemia.
- On average, the median pO_2 values in primary cancers of the uterine cervix are lower than those in the normal cervix.
- Many cervical cancers contain hypoxic tissue areas (at least 60% in SCC).
- There is no characteristic topological distribution of O_2 tensions within cervical cancers.
- Tumor-to-tumor variability in oxygenation is greater than intratumor variability.
- Tumor oxygenation is independent of various patient demographics (*e.g.*, age, menopausal status, and parity).
- Anemia (found in ~30% of patients at diagnosis) considerably contributes to the development of hypoxia, especially in low-flow tumor areas.
- In cervical cancers of moderately/severely anemic patients, hypoxic areas are more frequently found than in nonanemic patients.
- Tumor oxygenation and the extent of hypoxia are independent of clinical size, FIGO stage, histological type (SCC *vs.* AC), grade and lymph node status.
- Tumor oxygenation is weakly dependent on the pathological tumor stage (pT stage).
- Local recurrences of cervix cancers have a higher hypoxic fraction than the primary tumors.
- Hypoxia in cervical cancers is of prognostic significance in many investigations (see Table 2).

OXYGENATION STATUS OF PRIMARY AND METASTATIC CANCERS OF THE HEAD AND NECK

The accessibility of primary and metastatic SCC of the head and neck for tumor oxygenation assessment has meant that these tumors have received much attention, with a large number of studies already documented (Table 3).

Reliable O_2-sensitive polarographic electrodes for measurement of O_2 tensions in head and neck cancers were first used by Gatenby *et al*. (43, 44). These authors convincingly demonstrated that hypoxia in advanced tumors was associated with a poor prognosis.

Relevant oxygenation data derived from primary head and neck tumors (5–7, 11, 16, 38, 74, 110, 112, 122) and from metastatic lesions of SCC of the head and neck (5–7, 11, 16, 32, 39, 72, 74, 76, 83, 100, 112, 113, 116, 122) were summarized in 2001 (126). The pO_2 measurements published between 1988 and 2000 confirm in essence the oxygenation pattern described for cancers of the uterine cervix. For *primary tumors,* the following descriptive parameters for the oxygenation status (pooled data) have been calculated: overall median pO_2 = 13 mm Hg and overall HF 2.5 = 19%. A pronounced interinstitutional difference becomes obvious when the data from several centers are compared, with less hypoxic tumors being reported by the Stanford group (122) and Durham (Duke) documenting more patients with more hypoxic tumors (11, 16).

For *metastatic tumors,* the following descriptive parameters for the oxygenation status have been assessed (pooled data collected between 1993 and 2000): overall median pO_2 = 13.5 mm Hg and overall HF 2.5 = 17%. On comparing these latter data with pO_2 parameters of primary tumors, it becomes evident that no obvious difference between the oxygenation status of primary and metastatic tumors of the head and neck exists. Again, pronounced interinstitutional differences can be seen with Stanford reporting relatively more patients with less hypoxic tumors and Durham more patients with more hypoxic tumors.

An updated summary of all major studies on the oxygenation status of head and neck cancers and on the relationship between pretreatment pO_2 measurements and survival in advanced tumors after primary radiotherapy has been published recently (96). In Table 3, tumor oxygenation data and survival in 397 primary head and neck cancers as summarized by Nordsmark *et al*. (96) and updated by results communicated more recently are shown (17, 80).

As was the case for cancers of the uterine cervix, pO_2 data clearly show that an optimal Hb level with regard to the median pO_2 values of head and neck cancers is seen at cHb values of between 12.5 and 14.5 g/dL (7, 96, 136, 138, 140). Furthermore, when comparing the parameters of the oxygenation status, there is a trend suggesting that cancers of the head and neck may be slightly better oxygenated than cervical cancers

TABLE 3. PRETHERAPEUTIC OXYGENATION STATUS OF HEAD AND NECK CANCERS[a] AND PROGNOSTIC SIGNIFICANCE OF TUMOR HYPOXIA (n = NUMBER OF PATIENTS)

					Prognostic significance of tumor hypoxia		
Center	n	*Median pO_2 (mm Hg) [range]*	*HF 2.5 (%)*	*HF 5 (%)*	*Endpoint*	*Oxygenation parameter*	*References*
Halle/Munich	125	9 [0–59]		33	OS	HSV[b]	31
Durham	86	5 [0–60[		51	DFS, OS, LC	$pO_2 < 10$ mm Hg	11, 16, 96
Aarhus	67	13 [0–54]	22	32	LC	$pO_2 < 2.5$ mm Hg	92, 93
Stanford	65	12 [0–45]		25			80
Heidelberg	44	7 [0–60]	25	44	OS	$pO_2 < 2.5$ mm Hg	107, 108
Paris	40	9 [0–55]	22	41			72, 83, 96
Stanford	37	19 [0–77]	16	21	LC	median pO_2 (trend)	1
Heidelberg	37	3	45	58		No evidence	26, 27
Stanford	25	18 [0–51]	0	2		No evidence	122
Aachen	20	11 [0–22]	32	44			25
Las Palmas	16	16	20	29			17
Leipzig/Aachen	16	10					111
Erlangen	14	16	19	35			116
Overall	592	10	21	32			

[a]Tumor oxygenation was measured in neck node metastases (predominantly) and in primary cancers.

[b]Hypoxic subvolume calculated as the product of the total tumor volume and the relative frequency of hypoxic pO_2 readings <5 mm Hg.

There may be some overlap in patients reported from the same institution.

Empty boxes indicate lack of suitable information.

(Tables 2 and 3), due primarily to the smaller hypoxic fractions found in head and neck tumors.

Hypoxia in head and neck cancers is of prognostic significance in many investigations (see Table 3).

OXYGENATION STATUS OF BREAST CANCERS

Many breast cancers have hypoxic tissue areas that are heterogeneously distributed within the tumor mass. Mean and median O_2 tensions (pO_2) obtained from different pathological stages and histological grades are on average distinctly lower than in the normal breast or in fibrocystic disease (Fig. 2). Oxygen tensions measured in normal breast tissue revealed a mean (and median) pO_2 of 65 mm Hg, whereas in breast cancers of stages T1b–T4, the median pO_2 was 28 mm Hg (143). Nearly 60% of the breast cancers investigated exhibited pO_2 values $\leq$ 2.5 mm Hg (*i.e.*, tissue areas with less than half-maximum radiosensitivity). In contrast, in the normal breast, pO_2 values $\leq$ 12.5 mm Hg were not found (143). In our earlier studies on breast cancers, bimodal pO_2 distribution curves were obtained, indicating a relevant contribution of pO_2 readings from the stromal compartment of breast cancers in these measurements, possibly due to inflammation. A contribution of pO_2 readings in the stromal compartment is substantiated by the finding that pO_2 readings under ultrasound guidance are on average lower (Fig. 2). Thus, unintentional pO_2 measurements in the stromal compartment of breast cancer can cause a shift in the pO_2 histogram to higher values (132, 137).

When tumors of different sizes are compared, there is no evidence of a correlation between the median pO_2 and the diameter of the tumor. This implies that the oxygenation in breast cancers and the occurrence of hypoxia and/or anoxia do not correlate with clinical stage (131, 132, 134, 143). Similarly, there is no association between tumor size and blood flow (46, 149). In addition, there is substantial evidence that the oxygenation patterns do not correlate with either histology (37, 143) or a series of other clinically relevant parameters, such as hormone receptor status, parity, menopausal status, and smoking habits (143). In contrast, a significant correlation between the mean pO_2 values, fraction of hypoxic pO_2 readings, the degree of differentiation, and prognostic markers was found in a subsequent study (60).

No significant differences were found between pre- and postmenopausal patients, between lobular and ductal carcinomas, and between tumors in the upper *versus* lower quadrants. No correlation between pathological staging or grading and the number of pO_2 readings at zero level, the pO_2 readings from 0 to 2.5 mm Hg, the mean or median pO_2, and the 10^{th} and 90^{th} percentiles could be detected. Up to now, no correlations have been found between the oxygenation status of the tumors and the extent of necrosis or fibrosis (information based on qualitative evaluation). There is marked tumor-to-tumor variability, even when tumors of the same clinical size, stage (pT2), grade (G2), and histology (ductal carcinomas) are compared (143). For this reason, tumor oxygenation is not predictable in terms of clinical size, stage, grade, or histological type.

The pretreatment oxygenation status in breast cancers tended to be poorer and the occurrence of hypoxia and/or anoxia was more frequent in anemic patients than in women with cHb $>$ 12 g/dL (142, 145).

TABLE 4. PRETHERAPEUTIC OXYGENATION STATUS OF BREAST CANCERS (n = NUMBER OF PATIENTS)[a]

Center	n	*Median pO_2 (mm Hg)*	*HF 2.5 (%)*	*HF 5 (%)*	*HF 10 (%)*	*References*
Munich	41	2	68	87		104
Mainz/Leipzig	37	6	25	49		142
Berlin[b]	32	44	7		17	60
Mainz	18	28	6	15	32	143
Mannheim	18	23	8	16	26	109
Durham	18	21		35		147
Leipzig	15	10	30	45	50	145
Durham	15	6				10
Durham	13	14				61
Oxford	5	24	5		13	37
Overall	212	10[c]	30[c]	47[c]	50[c]	

[a]No convincing data on the prognostic significance of tumor hypoxia in breast cancers available so far.
[b]General anesthesia, inspiratory O_2 concentration = 30%.
[c]Only pO_2 readings obtained under ultrasound guidance included.
There may be some overlap in patients reported from the same institution.
Empty boxes indicate lack of suitable information.

When comparing pO_2 data of breast cancers measured with the computerized pO_2 histography system by different institutions, significant inexplicable interinstitutional variation in the oxygenation status observed (Table 4).

As was the case with primary tumors, the oxygenation of metastatic lesions is generally heterogeneous and lower than that of normal tissues at the site of metastatic growth. Metastatic lesions of breast cancers tended to have a poorer oxygenation status than the primaries. Local recurrences of breast cancers also seem to have a higher hypoxic fraction than the primary tumors, although this information is based on only one communication (39).

OXYGENATION STATUS OF SOFT TISSUE SARCOMAS (STS)

As was the case with the tumor entities listed above, the oxygenation of STS was significantly lower than that of the sub-

TABLE 5. PRETHERAPEUTIC OXYGENATION STATUS OF SOFT TISSUE SARCOMAS AND PROGNOSTIC SIGNIFICANCE OF TUMOR HYPOXIA (n = NUMBER OF PATIENTS)

						Prognostic significance of tumor hypoxia		
Center	n	*Median pO_2 (mm Hg) [range]*	*HF 2.5 (%)*	*HF 5 (%)*	*HF 10 (%)*	*Endpoint*	*Oxygenation parameter*	*References*
Durham	45	10				DFS	$pO_2 < 10$ mm Hg	10
Durham	34	6 [0–68]				DFS	median pO_2	15
Aarhus	31	19 [1–58]				DFS, OS	$pO_2 < 19$ mm Hg	94
Durham	30	10				DFS	$pO_2 < 10$ mm Hg	14
Durham	28	10						24
Aarhus	25	22 [1–58]	5					98
Aarhus	22	18		17				97
Aarhus	18	23		10				95
Durham	15	18		31				13
Durham	9	21 [2–38]	19	29	44			12
Munich/Essen	8			10				39
Munich/Essen	7[a]		8					87
Aarhus	6	10 [1–34]	18					8
Philadelphia	5	4	45	57	74			34
Overall	283	14	13	21				

[a]Recurrent soft tissue sarcomas.
There may be some overlap in patients reported from the same institution.
Empty boxes indicate lack of suitable information.

cutis (95) or of benign tumors [*e.g.*, lipomas or Schwannomas (8)]. Tumor oxygenation was markedly heterogeneous (97, 98), with the variation in oxygenation between tumors being significantly greater than that within tumors (12, 95, 97). No correlation was found between the oxygenation status and either volume, histopathology, grade of malignancy, p53 status, and other tumor features or several patient characteristics (94, 97). In addition, no association with electrode position within tumors (*i.e.*, between the depth from the tumor surface and measured pO_2 values) was seen (12). In contrast to the tumor entities described above, no correlation with Hb levels were found (97). Again, a pronounced interinstitutional variation becomes obvious when data from several centers are compared, with less hypoxic tumors reported by the Aarhus group (95, 98) and the group from Philadelphia (34). In addition, pronounced intrainstitutional differences are reported by the Duke (Durham) group when the median pO_2 is considered [6 *vs.* 21 mm Hg; (12, 14, 15)]. Factors that might be responsible for these differences have not yet been determined.

Hypoxia in STS is of prognostic significance in investigations involving large numbers of patients (Table 5).

OXYGENATION STATUS OF BRAIN TUMORS

Studies performed so far on *primary brain tumors* convincingly show the existence of areas of severe hypoxia in both high and low grade brain tumors (9, 22, 65, 88, 123, 127).

As was also seen in the other types of tumors characterized so far, pO_2 values varied widely among patients (66) and were distinctly lower than in the normal brain tissue (105, 123). Hypoxia was not an artifact of general anesthesia (as it also not in the before-mentioned tumor entities), since comparable hypoxic areas were also found in patients undergoing craniotomy under local anesthetics. An association between oxygenation status and clinical tumor size has so far not been found. There is evidence that hypoxia might be grade-dependent (19, 69, 88) with high-grade gliomas exhibiting poorer oxygenation status than low-grade tumors (Table 6).

Increasing hypoxia with increasing tumor aggressiveness and rapidity of growth was observed by Rampling *et al*. (105). In contrast, Evans *et al*. (36) failed to find correlations between oxygenation parameters (median pO_2, HF 2.5, HF 5, and HF 10) and histopathological grade.

In a mixed group of *metastatic brain tumors,* marked hypoxia was also a common finding (105). In five metastatic lesions within the brain (maximum tumor diameter: 38 mm), the median pO_2 was 10 mm Hg (range: 3–24 mm Hg), the hypoxic fraction of pO_2 values $\leq$2.5 mm Hg being 26% (range: 1.5–46.5%). From these data it may be concluded that metastatic lesions in the brain do not substantially deviate from primary tumors in terms of oxygenation status.

PRETHERAPEUTIC OXYGENATION STATUS OF MISCELLANEOUS TUMORS

Quantitative data on the oxygenation status of several other tumor types as assessed by pO_2 histography—and not yet mentioned in this article—are compiled in Table 7. Again, there is clear evidence that the oxygenation of these tumors is distinctly poorer than that of the respective normal tissues (Table 8). For *prostate cancers*, there are again pronounced inter-institutional

Table 6. Pretherapeutic Oxygenation Status of Primary Brain Tumors and Prognostic Significance of Tumor Hypoxia

Center	n	*Median pO_2 (mm Hg) [range]*	*HF 2.5 (%)*	*HF 5 (%)*	*HF 10 (%)*	*References*
Philadelphia	26	22	16	25	40	36
New Haven	25	5[e]				69
	14[b]	3 [0–30]				
	11[c]	15 [0–40]				
New Haven[a]	23	11 [0–40]	40			19
	13[b]	6	48			
	10[c]	17	31			
Glasgow	15	9 [0–42]	42			105
	10[c]	7	38	45	59	
Philadelphia	12[c]	22	6	16	37	35
Las Palmas	3[b]	13		28	49	18
Overall	104	13	26			

n, number of patients.
[a]Mean arterial O_2 tension: 200 mm Hg.
[b]High-grade gliomas.
[c]Low-grade gliomas.
[d]Glioblastomas.
[e]No prognostic value of the median pO_2.
There may be some overlap in patients reported from the same institution. Empty boxes indicate lack of suitable information.

Table 7. Pretherapeutic Oxygenation Status of Miscellaneous Human Tumors (n = Number of Patients)

Center	n	*Median pO_2 (mm Hg) [range]*	*HF 2.5 (%)*	*HF 5 (%)*	*HF 10 (%)*	*References*
Prostate cancer						
Philadelphia	57	2 [0–68]				90
	55	10				89
Toronto	55	5 [0–57]		60		101
Philadelphia	13	21 [0–45]				23
	10	11 [2–38]	45	49		91
Vulvar cancer						
Mainz/Leipzig	29	11	25	40		145
	15[a]	13	25	37		141
	19[b]	11	25	45		
Vancouver	20	10	29			115
Non Hodgkin's lymphoma						
London	8	18	36		43	103
Malignant melanoma (metastatic)						
Paris	18	12	5	17	40	70
Lung cancer						
Cambridge	6	14	13	24	36	37
Stanford	20	17				79
Pancreatic adenocarcinoma						
Stanford	7[c]	2	59			68
Lund	1	2				45
Renal cell carcinoma						
Heidelberg (Australia)	3	10				77
Rectal carcinomas						
Heidelberg	14	32		10		62, 63
(Germany)	15	19				84
Liver tumors (metastatic)						
Heidelberg (Germany)	4	6			75	62, 63

[a]Primaries.
[b]Recurrencies.
[c]All patients were anemic.
There may be some overlap in patients reported from the same institution.
Empty boxes indicate lack of suitable information.

and intra-institutional variations which are not yet explained. With the exception of prostate cancer, the number of patients is rather low so that further discussion of the data here is not appropriate at this time.

Tumor oxygenation measurements in 28 tumors summarized by Aquino–Parsons *et al*. (4) are not included here, since 12 different histologies were listed, making a systematic evaluation impossible. The overall median pO_2 value for all 28 tumors was 24 mm Hg (range: 0–54 mm Hg).

CONCLUSIONS

Data obtained from 125 research articles using the pO_2 histography system for assessment of the oxygenation status in tumors have been considered in this review. Considering these data, it can be concluded that all types of solid tumors contain

Table 8. Oxygenation Status of Normal Tissues

Tissue	*Median pO_2 (mm Hg)*	*HF 2.5 (%)*	*HF 5 (%)*	*HF 10 (%)*	*References*
Pancreas	57	2			68
Breast	52	0	0	0	142
Rectal mucosa	52				62
Subcutis	51	0	0	4	142
Cervix	42	8	13	20	57
Kidney	31		3	8	77
Skeletal muscle	30				90
	25		4	12	144
Liver	30		5	13	63
Brain	24		3	13	127
	27		8	13	18

Empty boxes indicate lack of suitable information.

tissue areas that are severely hypoxic with great inter- and intra-institutional variations. Tumor hypoxia mainly results from inadequate perfusion and diffusion within tumors and from a reduced O_2 transport capacity in anemic patients. Hypoxic areas are heterogeneously distributed within the tumors. The development, existence, and extent of hypoxia are usually independent of a series of patient and tumor characteristics. Tumor oxygenation is, as a rule, poorer than that of the respective normal tissue. The oxygenation status of cancers of the cervix and of the head and neck, as well as oxygenation parameters of soft tissue sarcomas, may be independent adverse prognostic factors and may help to select patients for individual and/or intensified treatment schedules. The significance of tumor oxygenation as an adverse prognostic factor is most probably based on acquired treatment resistance and on hypoxia-induced malignant progression.

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ABBREVIATIONS

AC, adenocarcinoma; cHb, hemoglobin concentration; DFS, disease free survival; DS, distant spread; Hb, hemoglobin; HF, hypoxic fraction; H & N, head and neck; LC, local control; OS, overall survival; PFS, progression-free survival; pO_2, oxygen partial pressure, oxygen tension; SCC, squamous cell carcinoma; HSV, hypoxic subvolume; STS, soft tissue sarcoma; SC, subcutis.

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