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Local spread of cervical cancer revisited: A clinical and pathological pattern analysis

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ABSTRACT

Background. Local tumor spread of cervical cancer is currently considered as radial progressive intra- and extracervical permeation. For radical tumor resection or radiation the inclusion of a wide envelope of tumor-free tissue is demanded. However, this concept may lead to considerable treatment-related morbidity and does not prevent local relapse. We propose an alternative model of local tumor propagation involving permissive compartments related to embryonic development.

Methods. We analyzed local tumor spread macroscopically and microscopically in consecutive patients with advanced cervical cancer and post-irradiation recurrences.

Results. Macroscopically, all 33 stage I B (>2 cm) tumors, 40 of 42 stage II tumors and 32 of 44 stage III B tumors were confined to the embryologically defined uterovaginal (Müllerian) compartment. Local tumor permeation deformed the uterovaginal compartment mirroring the mesenchyme distribution of the Müllerian anlage at the corresponding pelvic level in cases of symmetrical tumor growth. Tumor transgression into adjacent compartments mainly involved the embryologically related lower urinary tract. Compartmental transgression was associated with larger tumor size, paradox improvement in oxygenation and an increase in microvessel density. Post-irradiation pelvic relapse landscapes were congruent with the inflated Müllerian compartment. Microscopically, all locally advanced primary cancers and post-irradiation recurrences were confined to the uterovaginal and lower urinary tract compartments.

Conclusion. Cervical cancer spreads locally within the uterovaginal compartment derived from the Müllerian anlage. Compartment transgression is a relatively late event in the natural disease course associated with distinct phenotypic changes of the tumor. Compartmental tumor permeation suggests a new definition of local treatment radicality.

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Introduction

Standard treatment of surgical cancer is surgery for early disease and chemoradiation for more advanced tumors [1]. The basis for the local treatment of cervical cancer, with surgery as well as with radiation, is a conception of local tumor spread assuming radial progressive intra- and extracervical permeation favoring planes of low mechanical resistance with microscopic or occult disease preceding the macroscopic tumor front. The lateral paracervical tissue is assumed to represent the dominant route for extracervical local tumor propagation. Consequently, radical hysterectomy, the current surgical treatment standard aims to resect the cervical cancer with a tumor adapted margin of uninvolved paracervical tissue with special reference to the lateral parametrium [2]. However, despite adjuvant pelvic radiation in about every second operated case with early stage disease, local recurrence rates of 15% occur [1]. Extension of the parametrectomy does not improve the local control rate; it only increases treatment-related morbidity which is represented by a 20–40% rate of moderate and severe complications [3].

We argue that these relatively unfavorable clinical results and inconsistencies may challenge the current treatment principles. We have suggested an alternative concept of local tumor spread providing the basis for a different definition of local oncologic treatment radicality. Malignant solid tumors are confined for a relatively long phase during their natural course to a permissive compartment,

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which can be deduced from embryonic development as the final differentiation product of the corresponding anlage [4,5]. Compartment borders are primarily tumor suppressive. For transgression into adjacent compartments of different embryonic origin, phenotypical changes are necessary, which evolve relatively late during malignant progression. Local relapses arise from remnants of the compartment that remain in situ after treatment harboring or recruiting residual tumor (stem) cells.

We have identified the uterovaginal (Müllerian) compartment as the differentiation product of the Müllerian anlage, the paramesonephric–mesonephric complex connected to the deep urogenital sinus, in the adult female and reported its visualization by pelvic MRI and surgical exposition [4,5].

Indirect proof for the theory of compartmental tumor spread has been provided in early stage (IB – IIB) cervical cancer

1. by demonstrating that the removal of the uterovaginal compartment with intact borders with total mesometrial resection (TMMR) leads to excellent local tumor control without adjuvant radiation and irrespective of the metrical extension of the tumor-free margins [4,5];
2. by showing that local recurrences after standard radical hysterectomy arise and propagate within retained remnants of the Müllerian compartment [5].

Other investigators have meanwhile confirmed anatomical and conceptual aspects of our proposals by different methodological approaches [6,7]. Here, we add direct evidence for compartmental tumor spread by analyzing macroscopically and microscopically local growth patterns of advanced primary cervical cancer and post-irradiation local recurrences within anatomically intact pelves.

Patients and methods

During 2001–2006 consecutive patients with histologically proven cancer of the uterine cervix and clinically estimated tumor size >2 cm (defined as locally advanced disease) admitted to our center were invited to participate in a prospective study of tumor oxygenation. The trial was approved by the local ethics committee and informed consent was obtained from all patients. Patients were examined by gross and speculum inspection, vaginal and rectovaginal palpation, cysto- and rectoscopy under anesthesia. Core biopsies were taken under clinical guidance. The carcinomas were staged according to the FIGO rules. Tumor size was estimated clinically. In addition, the patients received pelvic MRI. MR imaging was performed with 1.5 T magnets (Siemens Medical Systems, Erlangen, Germany). Using surface coils and parallel imaging, sagittal and axial T2-weighted fast spin echo images, axial T1-weighted images pre and post gadolinium-diethylenetriamine pentaacetic acid, Gd-DTPA (0.1 mmol/kg body weight), T1-weighted axial fat-suppressed images after Gd-DTPA, and sagittal T1-weighted images after Gd-DTPA were acquired. Tumor oxygenation was measured with the Eppendorf histography system (Eppendorf, Hamburg, Germany) adhering to the standard procedure as developed and validated earlier [8]. This patient cohort was retrospectively analyzed for the macroscopic pattern of local tumor spread.

To develop pelvic relapse maps of cervical cancer recurring after curative chemoradiation we analyzed all consecutive patients with histologically proven post-irradiation pelvic relapses examined for potential surgical salvage treatment from October 2001 to July 2003. The group consisted of 9 patients with a median age of 51 years (range: 32–74 years). Eight patients had squamous cell carcinoma and one had adenocarcinoma. Stage distribution of the primary disease was II B $n=2$, III B $n=7$. Median time to relapse was 15 months (range: 12–448 months).

T2-weighted transverse pelvic MRI scans were used to delineate the recurrences and to determine the tumor volumes. Co-registration of the relapse volume data within the "Visible Woman" pelvic data set ("The Visible Human Project®", National Library of Medicine, Bethesda, Maryland, USA; www.ulm.nih.gov/research/visible_human.html) was done as described [5].

Since 2001 selected patients with locally advanced primary cervical cancer who were not candidates or refuted chemoradiation and patients with post-irradiation local recurrences were offered surgical treatment with laterally extended endopelvic resection (LEER) [9]. The surgical specimens of this patient cohort were investigated histopathologically for local tumor spread. Histopathological work-up of the LEER specimens was done in accordance with the general recommendations of the Cancer Committee of American Pathologists [10]. Histologic type and grade were determined according to the WHO classification. Tumor size was evaluated in all 3 dimensions. Neoplastic infiltration of the uterovaginal and adjacent tissues, the distance of the microscopic tumor front to all exposed resection margins, lymphatic space and venous vessel involvement, and lymph node metastases were assessed by two pathologists in H&E stained sections. Intratumoral microvascular density determination by CD34 immunohistochemistry was conducted as developed by Weidner et al. [11]. Microvessels were counted at a total magnification of ×200 within tumor "hot spots" located in the endocervical stroma and in the lamina muscularis of the urinary bladder. All slides were evaluated blindly by two observers using a multihead microscope.

Statistical analysis was performed with the SPSS 15.0 software. The Mann–Whitney U-test was used to compare two unpaired groups. For the comparison of two paired groups the Wilcoxon signed-rank test was applied. More than two unpaired groups were analyzed with the Kruskal–Wallis test. P-values less than 0.05 were considered to indicate statistical significance.

Results

148 consecutive patients with histologically proven advanced carcinoma of the uterine cervix defined by clinical tumor size >2 cm were prospectively studied regarding FIGO stage, tumor size, and oxygenation. One patient with simultaneous bladder cancer was excluded. The patient and tumor data are compiled in the Supplementary Table 1. This cohort of patients was analyzed for macroscopic local tumor spread using their MRI scans and cysto- and rectoscopy findings. In 3 patients MRI had to be substituted by CT. All 33 stage I B, 40 of the 42 stage II A, B tumors and 33 of the 44 stage III B tumors were confined to the uterovaginal compartment which is schematically shown in Fig. 1. Generally, local tumor spread of advanced stage cervical cancer as seen with MRI deformed the embryologically defined uterovaginal compartment by "inflation" or destruction (Fig. 2 a, b). Cases of symmetrical tumor propagation resembled the mesenchyme distribution of the corresponding section of the uterovaginal anlage. Bilateral transvaginal tumor spread was always directed dorsally towards the anterior mesorectum, transcervical tumor propagation could be traced dorsolaterally tangential to the lateral mesorectum. Only transcorporal tumor permeation showed a transverse direction approaching the pelvic walls. Fig. 3 compares typical tumor growth patterns with the corresponding mesenchyme distribution of the organ anlage at three transverse sectional levels: midvagina, cervix, and corpus. Transverse lateral tumor permeation from the cervix towards the pelvic wall, currently assumed as the main route of local tumor propagation, was never observed. The MRI correlation of cervical cancer clinically infiltrating the pelvic side wall was a fixation of the intracompartmental tumor to the parietal endopelvic fascia at the level of the levator ani muscle or at the sciatic foramen in all but one of 44 stage III B tumors (Figs. 2 c, d). Tumor transgression into adjacent non-Müllerian compartments involved predominantly the lower urinary tract and represented a late event in the disease course. No case of cervical cancer infiltrating the rectal mucosa could be demonstrated by rectoscopy. MRI found signs of

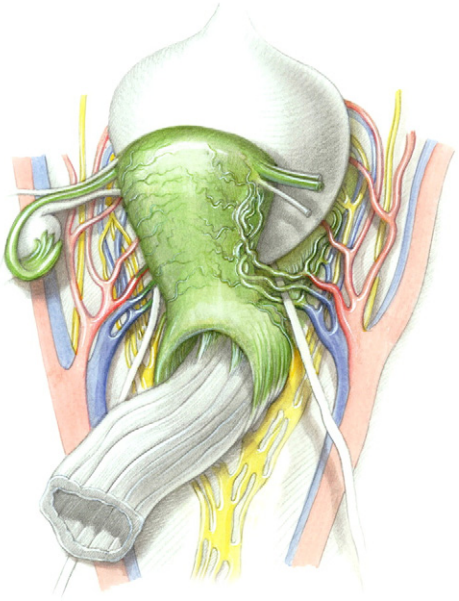

Fig. 1. Graphical representation of the uterovaginal compartment established as the differentiation product of the Müllerian anlage in the female pelvis. In this drawing the pelvic peritoneum, the right distal adnexal structures and all fatty and lymphatic tissue have been omitted to clarify the topographic anatomy. The uterovaginal compartment is highlighted in green.

cervical cancer transgression into the rectal, lateral parietal, and peritoneal compartments in 6, 5, and 3 patients (Fig. 4). However, cystoscopy unequivocally identified 34 tumors transgressing into the bladder compartment, 17 cases showed gross tumor infiltration of the bladder mucosa and 17 cases demonstrated bullous edema with pathological microvessels indicative for tumor infiltration of the bladder muscle. No carcinoma classified as stage I B and only two stage II B carcinomas had transgressed into the lower urinary tract. Seven of the 44 stage III cases and 23 of the 28 stage IV cancers involved the bladder compartment. All 19 cases of IV A tumors transgressed into the lower urinary tract.

Median tumor pO_2 values decreased with increasing stages I B to III B along with increasing tumor sizes. Unexpectedly, in stage IV A carcinomas the median pO_2 value increased although tumor sizes were maximal (Figs. 5 a, b). We investigated this paradox "re-oxygenation phenomenon" by comparing the oxygenation profiles of all locally advanced tumors stages III and IV with and without bladder involvement (i.e., infiltration of the bladder mucosa and muscle). The 30 tumors with signs of transgression into the bladder compartment had significantly higher median pO_2 values than the 42 tumors without transgression: 5.5 mm Hg (range: 0–36) vs. 4 mm Hg (range: 0–27) $p = 0.026$ (Figs. 5 c, d). Selecting only squamous cell carcinomas for that comparison raised the level of significance: 7 mm Hg (range: 2–36) vs. 3.8 mm Hg (range: 0–27) $p = 0.003$ (Figs. 5 e, f). The improvement in oxygenation in tumors transgressing into the bladder compartment despite an increasing tumor mass indicates a phenotype of locally advanced cervical cancer different from tumors confined to the uterovaginal compartment.

We also studied the pattern of pelvic recurrences of cervical carcinoma after curative (chemo-)radiotherapy. Frequency-weighted pelvic relapse maps were generated from a cohort of 9 unselected patients with histologically proven post-radiation recurrences. Median tumor volume was 15 cm^3, range 1–117 cm^3. The co-registration of recurrences from multiple patients within the same anatomical reference provides clues for the tumor permeation of cervical cancer recurring after primary chemoradiation in an anatomically intact pelvis. Fig. 6 shows that post-radiation recurrent cervical cancer

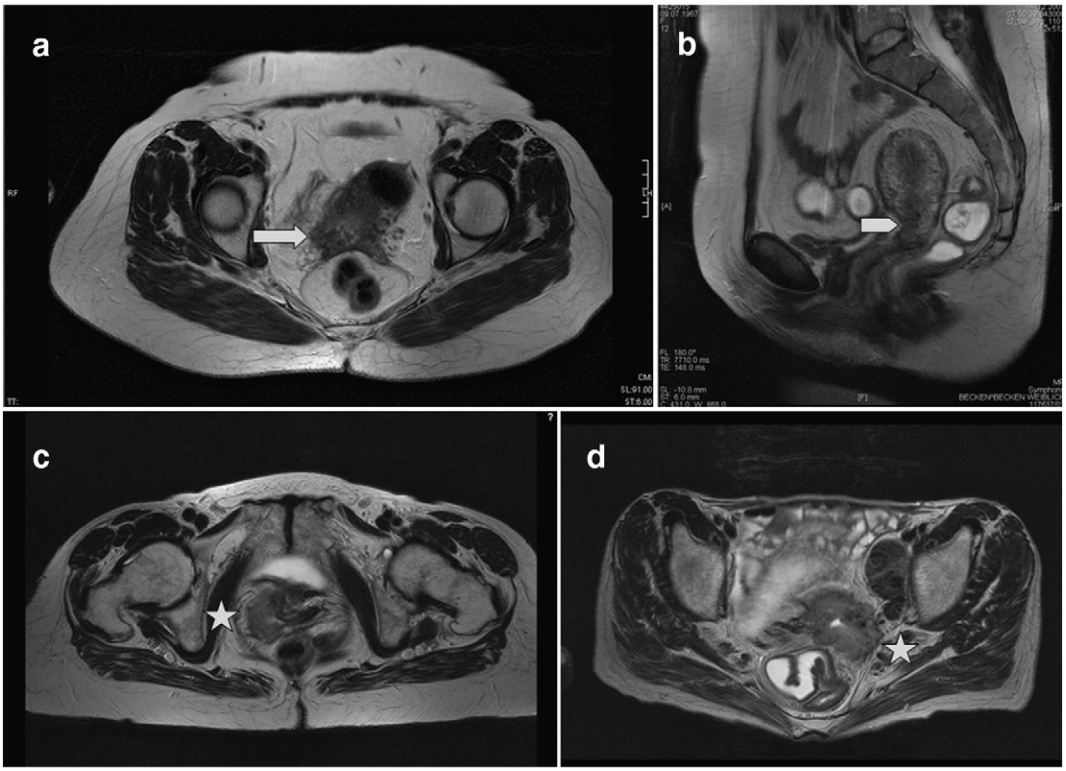

Fig. 2. Pelvic MRI scans demonstrating local permeation of cervical cancer by inflation (a) or destruction (b) of the uterovaginal compartment. The neoplastic tissue expansion is indicated by an arrow, the tissue defect by an arrowbar. c, d: MRI correlations of cervical cancer with clinical pelvic wall involvement. The subperitoneal tumor macroscopically still confined to the uterovaginal compartment is fixed to the endopelvic fascia (stars) at the level of the levator ani muscle (c) or at the level of the sciatic foramen (d).

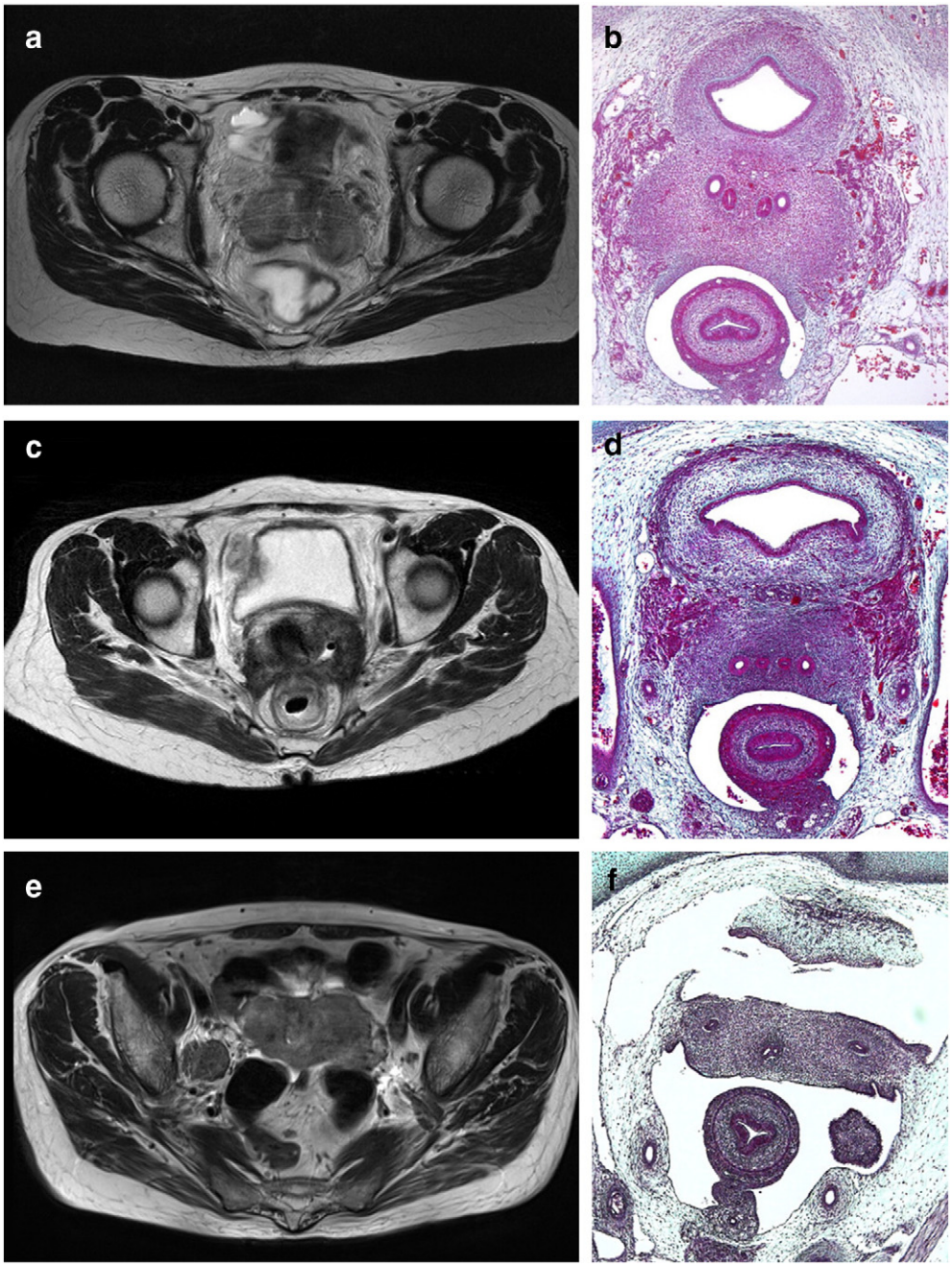

Fig. 3. Comparison of symmetrical neoplastic expansion of the uterovaginal compartment shown in pelvic MRI scans of patients with cervical cancer at three transverse levels (a, c, e) with histological sections of the Müllerian anlage at corresponding pelvic levels in a female 9 weeks old embryo (b, d, f). Transverse vaginal (a, b), cervical (c, d), and corporal (e, f) planes. The histologic work up of the embryonic tissue has been described earlier [5]. 5 μm thick transverse pelvic sections were stained with azocarmine, aniline blue, orange 6 and photographed at ×100 magnification.

propagates macroscopically within the Müllerian compartment. Macroscopic transgression into adjacent compartments was detected in 2 of the 9 recurrent tumors. Two transgressing tumors involved the bladder compartment, in one of them additional infiltration of the rectum muscularis was diagnosed.

Since 2001, 21 consecutive patients underwent LEER for previously untreated locally advanced primary and post-irradiation recurrent cervical cancer in anatomically intact pelves. The patient and tumor characteristics of 11 patients with primary and 10 patients with recurrent disease are listed in Tables 2 and 3 of the supplement. Histopathological assessment showed that all 21 tumors were resected with microscopically tumor-free margins (R0). The tumors involved the uterovaginal compartment in all cases and adjacent regions of the lower urinary tract in 90% (19/21) of the cases. Six tumors infiltrated the mucosa of the bladder. The perirectal fatty tissue was infiltrated in only one locally advanced primary and in two recurrent carcinomas, one relapse infiltrated the muscularis of the rectum. There was no microscopic involvement of the rectal mucosa, peritoneum or any lateral structure such as the endopelvic fascia or internal iliac vessel system. Urinary tract infiltration was multifocal and associated with an apparent increase of intratumoral microvessels (Fig. S1). In 7 of the 9 previously untreated primary squamous

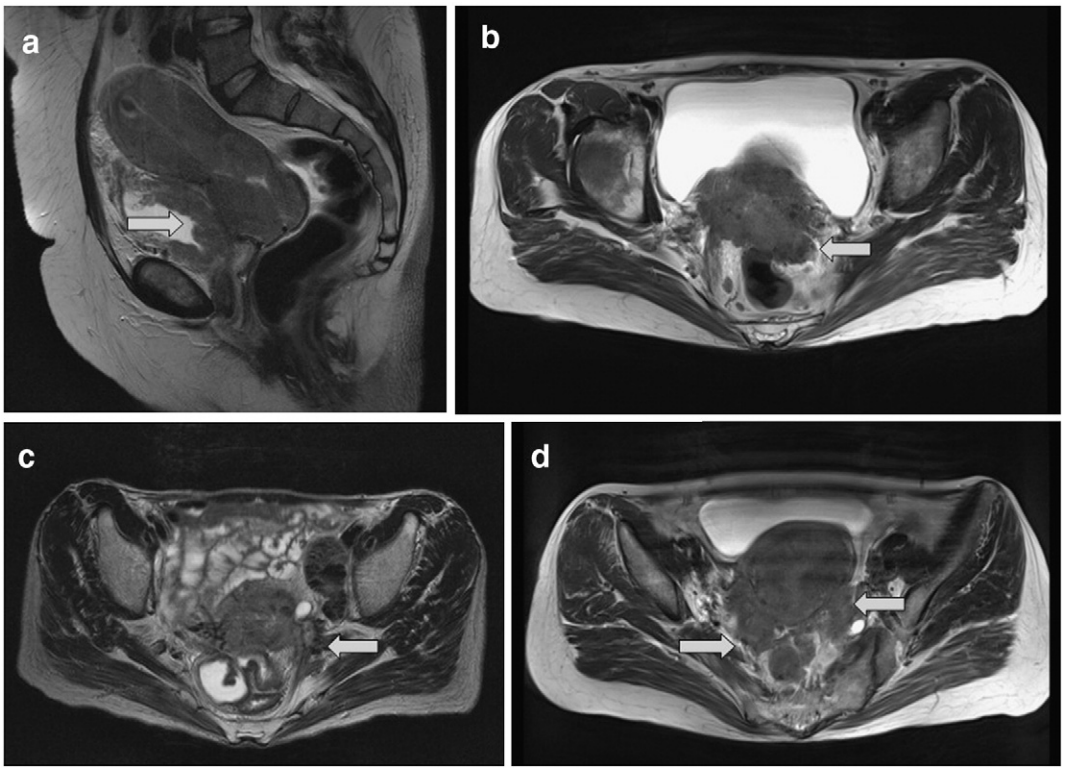

Fig. 4. MRI demonstration of advanced cervical cancer transgressing into the bladder (a), mesorectum (b), pelvic wall (c), and peritoneum (d). Arrows indicate sites of extracompartmental local tumor propagation.

cell carcinomas of the uterine cervix transgressing into the bladder, tumor microvessel density (TMVD) was higher within the vesical extension as compared to their uterovaginal site of propagation. Median TMVD was 63 (range 39–123) within the bladder and 49 (range 37–156) within the uterovaginal compartment.

Discussion

Essential results of this study challenge the current view of local spread of cervical cancer which assumes radial progressive intra- and extracervical tumor permeation. This model of local tumor spread can neither explain the dominance of bladder involvement as compared to the much less frequent infiltration of the rectum, peritoneum, and parietal endopelvic fascia nor the "re-oxygenation phenomenon" associated with clinical signs of bladder infiltration. Likewise, subperitoneal transverse parametrial tumor propagation to the lateral pelvic wall at the level of the cervix was never observed with MRI. This route of local tumor spread could only be detected in the few cases of *transcorporal* propagation of cervical cancer within the broad ligament in the peritoneal part of the female pelvis. Our results, however, support a concept of tumor permeation within the embryologically deduced uterovaginal (Müllerian) compartment. Previously, we have demonstrated the representation of the Müllerian compartment both in high resolution MRI and by surgical exposition [4,5]. We now show that pelvic MRI of locally advanced primary cervical carcinomas always demonstrated the major tumor mass within the uterovaginal compartment which was inflated or partially destroyed by the neoplasm. 98% of stage III B tumors clinically diagnosed as involving the pelvic side wall by parametrial tumor permeation were laterally restricted to the Müllerian compartment without evidence of infiltration of the parietal endopelvic fascia. Cases with symmetrical tumor involvement mirrored the mesenchyme distribution of the Müllerian anlage at the corresponding level within the pelvis. This congruence is confirmed by the pelvic relapse landscapes we generated from cervical cancer recurring after curative chemoradiation. In post-irradiation pelves the topographic pelvic anatomy is retained. Due to the radiation-induced tumor bed effect [12], neoplastic volumes are diminished compared to the primary disease of advanced malignant progression. The relatively small tumor masses facilitated their delineation and co-registration within the unit pelvis to demonstrate the spatial propagation of cervical cancer. As with primary disease, the spatial distribution of the post-irradiation recurrent tumors is not in line with a radial progressive model of tumor permeation. Neither is the idea of transverse tumor propagation substantiated by our results.

This study confirms that the infiltration of adjacent non-Müllerian tissues by cervical cancer is a relatively late event in the natural course and compartmental transgression is associated with phenotypic changes of the tumor. Compartment transgression was observed in 5% of stage II and in 27% of stage III tumors. Transgressing tumors exhibited the largest sizes. A phenotypic change detected with tumors infiltrating the (non-Müllerian) bladder compartment is represented by the paradox "re-oxygenation phenomenon". The fact that transgressing primary and post-irradiation recurrent cervical cancer infiltrated mainly the bladder may be explained by the embryological kinship of the Müllerian system with the lower urinary tract. The mesonephric and paramesonephric tissues are both derived from intermediate mesoderm. The mesonephric system participates both in the development of the urinary and the genital tracts.

The histopathological investigation of the patients treated with LEER for locally advanced primary and post-irradiation recurrent cervical cancer supports the macroscopic findings of local tumor permeation. Although tumor fixation to or involvement of parietal tissues at the site of the sciatic foramen has been considered as contraindication for treatment with LEER, the majority of tumors operated on were fixed to the pelvic side wall at the level of the

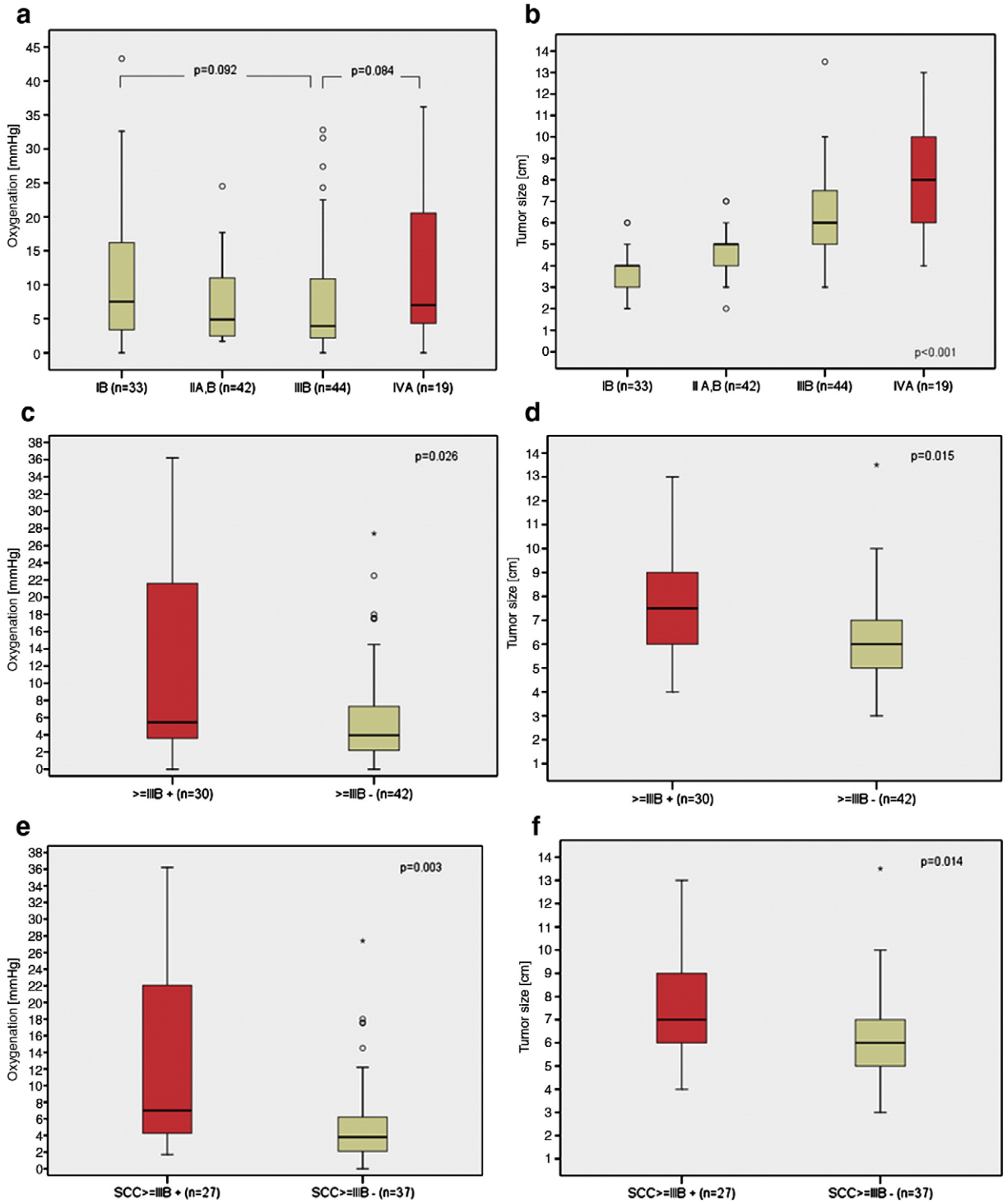

Fig. 5. Box plots showing median pO_2 values and tumor sizes of: a, b: cervical carcinomas related to FIGO stage; c, d: stage ≥ III B tumors with (≥ III B+) or without (≥ III B−) transgression into the bladder; e, f: stage ≥ III B squamous cell carcinomas with (SCC ≥ III B+) or without (SCC ≥ III B−) transgression into the bladder. Transgression into the bladder is associated with an increase in oxygenation despite larger size, whereas intracompartmental growth is associated with a decrease in oxygenation.

levator ani muscles. The selection process cannot explain the preference for tumor transgression into the lower urinary tract compartment. Likewise, the lateral confinement of the tumors to the uterovaginal and lower urinary tract compartments was substantiated by the fact that involvement of the endopelvic fascia or adjacent striated pelvic wall and floor muscles was never detected.

The apparent increase of microvessel density of advanced squamous cell carcinoma of the uterine cervix at the sites of bladder infiltration may be causatively involved in the "re-oxygenation phenomenon". One can speculate that compartment transgression enables the tumor to tap another vascular territory in addition to the one within the permissive compartment. However, our study was not

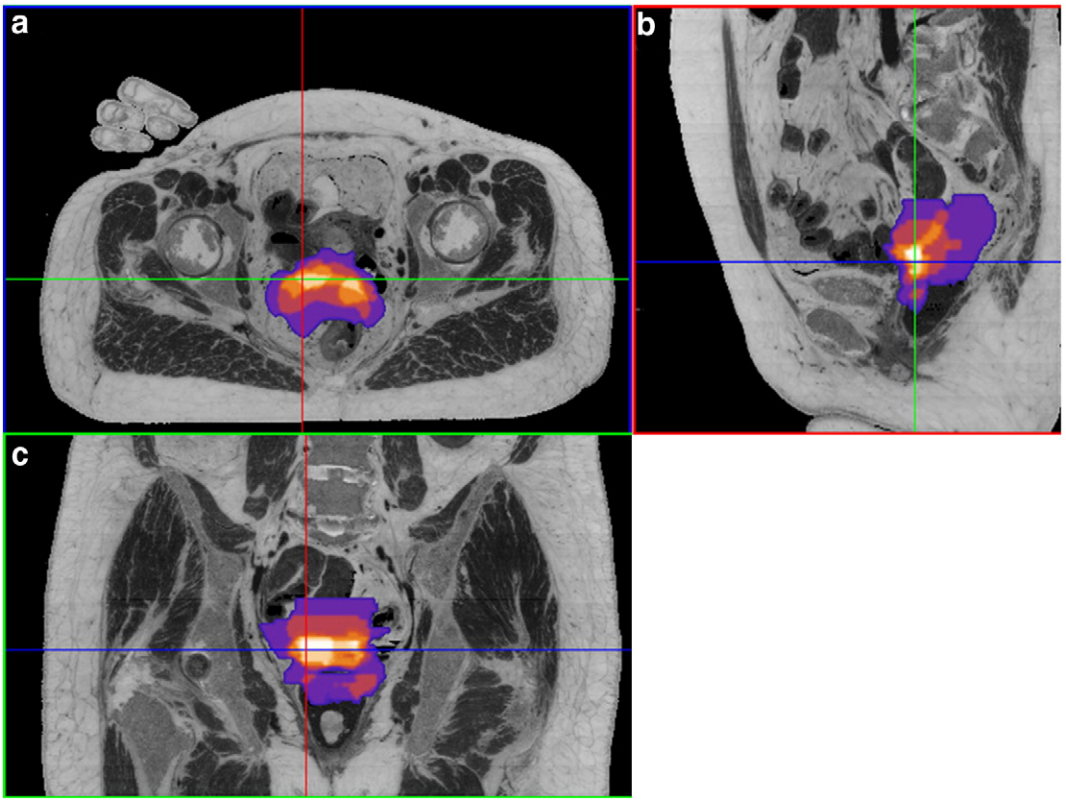

Fig. 6. 3-D pelvic relapse map ("landscape") obtained from 9 unselected consecutive patients with cervical cancer recurring after curative chemoradiation. Major tumor mass is confined to the embryologically deduced uterovaginal compartment at the cervical level. Representative transversal (a), sagittal (b), and coronal (c) planes. Relapse occurrence frequency is color-coded from blue indicating minimal frequency with at least one case via purple and red to bright yellow highlighting the maximum number of overlapping occurrences. Minimum frequency is one, maximum frequency is five for this map.

designed to investigate the pathomechanisms of tumor oxygenation and perfusion.

Limitations of our study are represented by the methodological uncertainties of the diagnostic procedures applied for macroscopic investigation and the relatively low number of patients with advanced disease available for microscopic assessment. However, diagnostic inaccuracy to be expected for MRI and endoscopy does not appear to bias the main insights obtained from our investigation. The fact that both the macroscopic and the microscopic evaluation led to the same results in terms of extracompartmental tumor involvement of advanced disease fosters the theory of embryologically defined compartmental tumor permeation.

The results of this study may have significant clinical implications with regard to cervical cancer treatment. They confirm the call for resection of the embryologically defined uterovaginal compartment for early cervical cancer instead of applying the treatment principle of wide radial paracervical margins [2]. In the surgical treatment of patients with locally advanced primary cancer that are not candidates for chemoradiation and for the salvage of post-irradiation persistence or recurrent disease, resection of both uterovaginal and lower urinary tract compartments is usually necessary, but the rectum may be retained if the intact compartment border can be exposed. Tumor fixation at the pelvic wall can no longer be regarded as a general contraindication for surgical treatment as these clinical features may represent fibrotic adherence of the tumor still confined to the uterovaginal compartment with the parietal endopelvic fascia at the levator ani level. Laterally extended endopelvic resection (LEER) including the en bloc removal of the pelvic floor and side wall muscles to assure the complete multicompartmental extirpation has a high potential of local tumor control in these cases. The design of radiation target volumes with regard to the topography of the uterovaginal compartment instead of adding a metrically defined tissue envelope to the gross tumor volume may further improve the therapeutic index in the radiotherapy of cervical cancer.

Conflict of interest statement
None of the authors has any conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ygyno.2010.02.014.

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