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Interstitial fluid pressure

Peritumoral interstitial fluid flow velocity predicts survival in cervical carcinoma

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ABSTRACT

Background and purpose: High tumor interstitial fluid pressure (IFP) is associated with poor outcome in locally advanced carcinoma of the uterine cervix. We have recently developed a noninvasive assay of the IFP of tumors, and in this assay, the outward interstitial fluid flow velocity at the tumor surface (v_0) is measured by Gd-DTPA-based DCE-MRI and used as a parameter for IFP. Here, we investigated the independent prognostic significance of v_0 in cervical cancer patients given cisplatin-based concurrent chemoradiotherapy with curative intent.

Patients: The study involved 62 evaluable patients from a cohort of 74 consecutive patients (Stage IB through IIIB) with a median follow-up of 5.5 years.

Results: The actuarial disease-free survival (DFS) and overall survival (OS) at 5 years were 67% and 76%, respectively. Significant associations were found between v_0 dichotomized about the median value and DFS and OS, both in the total patient cohort and a subcohort of 40 Stage IIB patients. Multivariate analysis involving stage, tumor volume, lymph node status, and v_0 revealed that only v_0 provided independent prognostic information about DFS and OS.

Conclusion: This investigation demonstrates a strong, independent prognostic impact of the pretreatment peritumoral fluid flow velocity in cervical cancer.

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The interstitial fluid pressure (IFP) is in general higher in malignant solid tumors than in most normal tissues [1]. Tumor tissues typically show IFP values of 5–50 mmHg, whereas the IFP measured in normal tissues usually ranges from −3 to +3 mmHg. Experimental studies have revealed that the IFP may differ significantly among individual tumors of the same line, even when transplanted to the same site and being of the same size [2]. Clinical investigations have shown that the intertumor heterogeneity in IFP is substantial in all tumor types studied thus far, including lymphoma, cutaneous melanoma, breast carcinoma, head and neck carcinoma, and cervical carcinoma [3].

Preclinical studies have provided strong evidence that high IFP in tumors may be a significant therapeutic problem [1–4]. First, highly elevated IFP may cause low and heterogeneous uptake of conventional and macromolecular chemical therapeutic agents, leading to poor response to many forms of chemotherapy [5]. Second, tumor interstitial hypertension may lead to resistance to radiation therapy through hypoxia-dependent as well as hypoxia-independent mechanisms [6,7]. Third, high IFP in tumors may promote hematogenous and lymphogenous metastatic dissemination [8,9].

Clinical investigations have revealed that the IFP of the primary tumor may be an important prognostic parameter in locally advanced carcinoma of the uterine cervix [10–12]. In these investigations, high IFP was associated with poor disease-free survival independent of conventional prognostic factors, such as tumor volume, stage, and lymph node status. Patients with tumors with high IFP showed an increased probability of developing recurrences both locally within the irradiated pelvic region and at distant non-irradiated sites. Interestingly, Fyles et al. [12] observed that the independent prognostic effect of IFP for recurrence and survival was strong, whereas the independent prognostic effect of tumor hypoxia was of borderline significance and was limited to patients without nodal metastases.

Tumor IFP was measured invasively with the wick-in-needle method in these clinical investigations [10–12]. A noninvasive method for assessment of the IFP of tumors has recently been developed in our laboratory [13]. Because the IFP of tumors drops steeply to normal tissue values at the tumor surface, interstitial fluid oozes continuously out from tumors into the surrounding normal tissue [4,14]. Our IFP assay is based on the assumption that the velocity of this fluid flow is determined by the IFP drop at the tumor

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surface. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) with gadolinium diethylene-triamine penta-acetic acid (Gd-DTPA) as contrast agent is used to detect the peritumoral interstitial fluid flow. By using mouse xenograft models of several types of human cancer, we have demonstrated that the velocity of the fluid flow at the tumor surface (v_0) correlates strongly with tumor IFP [13]. Furthermore, we have shown that the v_0 of the primary tumor can be measured accurately in cervical cancer patients and that v_0 is higher in patients with pelvic lymph node metastases than in patients without lymph node involvement [13].

In the present work, a different cohort of patients was studied to investigate whether v_0 may be an important prognostic factor for the long-term outcome of locally advanced cervical cancer after definitive cisplatin-based concurrent chemoradiotherapy. The study confirmed that the primary tumor v_0 is higher in patients with than in patients without pelvic lymph node involvement and showed that v_0 has a strong prognostic effect for disease-free and overall survival, independent of stage, tumor volume, and lymph node status.

Materials and methods

Patients

Seventy-four previously untreated patients recruited to the chemoradiotherapy protocol for locally advanced cervical cancer (FIGO Stage IB through IIIB) at the Norwegian Radium Hospital between October 2004 and June 2007 were included in the study. A total of 12 patients were excluded from the analysis, 8 because of severe motion artifacts in the MR images and 4 because the peak signal intensity of the Gd-DTPA-enhanced rim used to measure v_0 was poorly defined. The characteristics of the remaining 62 patients are summarized in Table 1.

Standard diagnostics and staging involved T_2-weighted MRI, T_1-weighted MRI, and Gd-DTPA-based DCE-MRI of the pelvis in addition to gynecological examination and biopsy. Positron emission tomography and/or computed tomography were not carried out routinely.

All patients were treated with concurrent chemoradiotherapy with curative intent. External beam radiation therapy was given in 25 fractions during a period of 5 weeks to a total dose of 50 Gy to the primary tumor, parametria, and adjacent pelvic wall and 45 Gy to the rest of the pelvic region. In addition, 5–6 fractions of intracavitary brachytherapy with a dose of 4.2 Gy per fraction were given to Point A. Chemotherapy with cisplatin (40 mg/m^2) was given weekly with a maximum of 6 courses during the radiation therapy period.

Table 1
Patient characteristics (N = 62).

Characteristic	
Age, years	
Median	54
Range	27–81
Histology, #patients	
Squamous cell carcinoma	53
Adenocarcinoma	9
Volume, cm^3	
Median	42.7
Range	4.8–319
FIGO stage, #patients	
IB	5
IIA	3
IIB	40
IIIA	2
IIIB	12
Pelvic lymph node status, #patients	
Positive	29
Negative	33

The patients were followed up by clinical examinations every third month for the first 2 years and thereafter every sixth month. The primary endpoints were disease-free survival (DFS), defined as the time to relapse or death from any cause measured from the date of diagnosis, and overall survival (OS), defined as the interval from diagnosis to death from any cause. DFS and OS curves were generated by using the Kaplan–Meier method. Median follow-up was 5.5 years (range 1.7–7.3 years).

The investigations were approved by the regional committee of medical research ethics in southern Norway and were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient.

Magnetic resonance imaging

A 1.5-T whole-body scanner (Signa; General Electric) and a 4-channel phased-array surface coil were used for MRI. The entire pelvic region was scanned with an axial T_2-weighted fast spin echo sequence (TR = 4960 ms, TE = 84 ms, field of view: 20 × 20 cm^2, image matrix: 512 × 512, number of excitations: 1.5, slice thickness: 5 mm, slice spacing: 6 mm). DCE-MRI was carried out at a temporal resolution of 29 s by using an axial T_1-weighted spoiled gradient recalled sequence (TR = 160 ms, TE = 3.5 ms, α_{T1} = 90°, field of view: 20 × 20 cm^2, image matrix: 256 × 256, number of excitations: 1, slice thickness: 5 mm, slice spacing: 6 mm). Three T_1-weighted images were acquired before a bolus of 0.1 mmol/kg Gd-DTPA was administered, and T_1-weighted images were recorded for 10 min after the Gd-DTPA administration. The MRI was carried out before treatment was initiated.

Tumor volume and metastatic status

Primary tumor volume and metastatic status were determined by examining MR images in the open source dicom viewer Osirix [15]. A region of interest (ROI) encompassing the tumor area was drawn in each T_2-weighted image, and tumor volume was reconstructed and calculated from these ROIs with a built-in function of Osirix. Metastatic status was assessed by examining the internal, external, and lower common iliac chains. A lymph node was scored as metastasis-positive when its shortest diameter in the T_2-weighted images was longer than 1.0 cm and the T_1-weighted images showed a contrast enhancement pattern similar to that of the primary tumor.

Assessment of peritumoral interstitial fluid flow velocity

The procedure used to measure peritumoral interstitial fluid flow velocity has been described in detail [13]. Briefly, the T_1-weighted image recorded immediately after the administration of Gd-DTPA showed a high-signal-intensity rim in the tumor periphery, and this rim moved outward with time. Movies showing the outward movement of the high-signal-intensity rim have been presented elsewhere [13]. The signal intensity across the rim was measured in line-shaped ROIs at different time points after the Gd-DTPA administration, as illustrated earlier [13]. The position of the peak signal intensity was identified by fitting a polynomial of the sixth degree to signal intensity data points calculated from four neighboring pixels by bilinear interpolation. The rim distance from the tumor surface (S), calculated from the position of the peak signal intensity, was measured as a function of time (t). The tumor surface (S = 0) was defined as the position of the peak signal intensity in the first T_1-weighted image recorded after the Gd-DTPA administration. Curves of $S(t) = S_0(1 - e^{-bt})$ were fitted to the data by regression analysis to determine S_0 and b, where S_0 is the