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Ultra-early Predictive Assay for Treatment Failure Using Functional Magnetic Resonance Imaging and Clinical Prognostic Parameters in Cervical Cancer

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Abstract

BACKGROUND—We prospectively evaluated MRI-parameters quantifying heterogeneous perfusion pattern and residual tumor volume early during treatment in cervical cancer, and compared their predictive power for primary tumor recurrence and cancer death with the standard clinical prognostic factors (CPFs). A novel approach of augmenting the predictive power of CPFs with MRI-parameters was assessed.

MATERIALS AND METHODS—Sixty-two cervical cancer patients underwent dynamic contrast-enhanced (DCE) MRI before and during early radiation/chemotherapy (2-2.5 weeks into treatment). Heterogeneous tumor perfusion was analyzed by signal intensity (SI) of each tumor voxel. Poorly-perfused tumor regions were quantitated as lower 10th percentile of SI (SI(10%)). DCE-MRI and three-dimensional (3D) tumor volumetry MRI-parameters were assessed as predictors of recurrence and cancer death (median follow-up, 4.1 years). Their discriminating capacity was compared with CPFs (stage, lymphnode status, histology) using sensitivity/specificity and Cox regression analysis.

RESULTS—SI(10%) and 3D-volume 2-2.5 weeks into therapy independently predicted recurrence (HR=2.6 [1.0-6.5], $P=.04$; HR=1.9 [1.1-3.5], $P=.03$, respectively) and death (HR=1.9 [1.0-3.5], $P=.03$; HR=1.9 [1.2-2.9], $P=.01$), and were superior to CPFs. The addition of MRI-parameters to CPFs increased sensitivity and specificity of CPFs from 71% and 51% to 100% and 71% for predicting recurrence; and from 79% and 54% to 93% and 60% for predicting death.

CONCLUSIONS—MRI-parameters reflecting heterogeneous tumor perfusion and subtle tumor volume change early during radiation/chemotherapy are independent and better predictors of

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Conflicts of Interest:

None

tumor recurrence and death than CPFs. Combination of CPFs and MRI-parameters further improves early prediction of treatment failure and may enable a window of opportunity to alter treatment strategy.

Keywords

DCE magnetic resonance imaging; Functional tumor imaging; Cervical cancer; Outcome prediction; Tumor heterogeneity; Tumor perfusion

INTRODUCTION

For advanced cervical cancer patients, the first-time radical treatment is the best and may be the only opportunity to achieve a complete cure. Unfortunately, favorable clinical prognostic factors (CPF) do not always translate into successful ultimate outcome, primary tumor control and disease-free survival. Advanced cervical cancer is a prime example of a disease in which the early prediction of ultimate treatment outcome is critical but has been challenging to achieve. Current gold-standard CPFs, stage,¹ lymphnode status² and histology,³ are established criteria for the selection of first-line therapy, but have been challenged by the variability of outcomes within each prognostic category.^{4, 5} The efficacy of radiation and chemotherapy generally cannot be reliably assessed until months after completion of all therapy by estimating tumor bulk using clinical palpation or by cervical cytology.⁶ Once treatment failure occurs, further treatment options are severely limited, salvage therapy is rarely effective and outcome is dismal.^{7, 8} Therefore individualized and therapy-specific predictors of primary tumor control and survival that are available *before or early* during a specific therapy regimen are needed to provide a window of opportunity to modify treatment strategy upfront and improve survival.

Ultra-early individualized outcome prediction, that is available within weeks of therapy start, critically depends upon the ability to quantify tumor heterogeneity and heterogeneous responses in patients with the same pre-treatment CPFs. Reliable clinically practical and non-invasive methods to effectively evaluate the heterogeneous therapy response in solid tumors have been elusive in clinical practice. Perfusion, reflecting the effectiveness of delivery of chemotherapy,^{9, 10} and oxygenation for radiation therapy (RT),^{11, 12} can be highly variable within each solid tumor. Essential information on this heterogeneity of perfusion¹³ during treatment, has not been incorporated into the treatment strategy despite its known profound impact on therapy outcome in cervical cancer.^{9, 10, 13-18} Furthermore, accuracy of tumor volume measurement, as a early response indicator during treatment, has also been limited because of the irregular tumor shapes and subtlety of early volume regression¹⁹.

The advancements in morphologic and functional imaging provide an opportunity to quantify each tumors' heterogeneity with dynamic contrast-enhanced (DCE) MRI,²⁰⁻²² and its heterogeneous early response to a specific ongoing treatment with improved three-dimensional (3D) MRI volume measurement.^{19, 23-25} In a prior exploratory study we have identified MRI-parameters of low tumor perfusion during early therapy and high 3D tumor volume as predictors of ultimate treatment failure.²⁶

The purpose of this study was to 1) validate and refine DCE- and 3D-volumetry MRI-parameters for the prediction of ultimate treatment outcome (recurrence and death) of the ongoing cytotoxic treatment in cervical cancer, 2) compare the discriminatory value of the MRI-parameters with that of the CPFs, and 3) develop a novel predictive paradigm by synergizing the prognostic power of the pre-treatment CPFs and those of the MRI-parameters obtained during early therapy.

MATERIALS AND METHODS

Patient Characteristics

Sixty-two patients with biopsy-proven advanced cervical cancer (excluding small cell/neuroendocrine histology), who were treated with RT and concurrent Cisplatin-based chemotherapy, were studied prospectively on an IRB-approved imaging protocol. Pre-treatment evaluations included routine work-up following FIGO guidelines.²⁷ Therapy consisted of standard RT in combination with concurrent weekly Cisplatin chemotherapy (40-50 mg/m²). RT included external beam radiation (dose to the pelvis, 31-66 Gy; mean, 46.2 Gy), combined with brachytherapy in all but 2 patients. Fifty patients had low-dose-rate brachytherapy (dose: 17-62, mean: 42 Gy), and 12 had high-dose-rate brachytherapy (30 Gy in 5 fractions). An average of 4.7 (range: 3-6) courses of Cisplatin were given with RT. In three patients, the Cisplatin was combined with 5-FU, and in three with Taxol.

MR Imaging

MRI was obtained pre-therapy and early during RT, after a dose of 20-25 Gy in 2-2.5 weeks and 2 cycles of chemotherapy. MRIs were performed with a 1.5 Tesla scanner and included sagittal T2-weighted imaging for 3D tumor volumetry measurement (Fig. 1) described in detail earlier.^{24, 28} DCE MRI was acquired for 158-168 seconds using a T1-weighted 3D-gradient-echo multi-slice sequence (TR/TE=12/5, Flip=25, Matrix=138×256, Partition=12, NEX=1, Slab=8.0cm) after 3 pre-contrast baseline acquisitions, and followed by a bolus of MRI contrast agent (0.1 mmol/kg) at 5 ml/second. To cover the entire tumor volume, the temporal resolution was reduced to 26-28 seconds, remaining appropriate for plateau phase SI assessment for each tumor voxel. The patients' therapy was not influenced by the MRI findings.

DCE Tumor Heterogeneity Analysis and 3D-Volumetry Analysis

The DCE-MRI imaging data sets were analyzed using the voxel-by-voxel analysis developed in our laboratory.²⁶ After contouring of the tumor, a DCE time-signal intensity (SI) curve was generated for each voxel in the tumor as described in detail earlier.²⁶ SI-voxel histograms (Fig. 1) of the voxel population within the entire 3-dimensional tumor region were generated to derive the mean SI (mSI), median SI, variance, standard deviation, kurtosis of the SI distribution, and SI percentiles (SI(%)). Based on our earlier exploratory study in a different patient population,²⁶ the 10th percentile of SI (SI(10%)) in the early-therapy phase, representing the proportion of low-perfusion regions within the heterogeneous tumor, was the strongest predictor of tumor control. Residual 3D tumor volume also showed a promising correlation with tumor control.

SI percentiles (SI(%)) in increments of 2.5% from SI(2.5%) to SI(40%), were generated to quantitate the degree and proportion of the poorly perfused low-DCE components within the tumor. An SI(%) was defined as the SI value, below which a given percentage of voxels within the histogram falls, e.g. SI(10%) is the SI value, below which the lowest 10% of voxels falls (Fig. 1). For volumetry, 3D-volume measurement was performed for each sequential MRI by delineating the tumor on all the T2-weighted images as described earlier.^{24, 28}

Outcome and Data Analysis

The outcome endpoint *primary tumor recurrence* (short: *recurrence*) was defined as tumor re-growth, persistence or progression in the uterus or pelvis after therapy completion. *Cancer death* (short: *death*) was defined as death from cervical cancer or cancer complications. Patients were evaluated post-therapy in 3- to 12-monthly intervals until death or data analysis. Median post-therapy follow-up of surviving patients was 4.1 (range, 0.2-7.9) years.

The DCE-MRI-parameters identified in the SI-voxel histogram and 3D-volume, and the CPFs were analyzed for their discriminating capacity in predicting recurrence vs. tumor control and death vs. survival. Optimal SI(%) parameters across the range of SI(%), and optimal parameter thresholds were determined by receiver operating characteristic (ROC) analysis. The threshold yielding the maximum $J_i = \{\text{sensitivity}_i + \text{specificity}_i - 1\}$ for predicting recurrence, where i represents each possible threshold, was selected. These same values were used as the threshold for cancer death sensitivity and specificity analysis. Sensitivity was calculated as the number of predicted positives divided by the number of true positives (7 recurrences, 14 deaths); specificity as predicted negatives divided by true negatives (55 recurrences, 48 deaths). Confidence intervals were calculated from the exact binomial distribution.

A combined CPF parameter categorized patients as *unfavorable* if they had at least one of lymphnode involvement, stage III or IV, or non-squamous histology. Patients not fitting any of these three criteria were categorized as *favorable*. Each CPF was weighted equally. To evaluate the combination of MRI parameters with and without CPFs, thresholds were determined from logistic regression models for recurrence. The probability value generating the maximum $\{\text{sensitivity} + \text{specificity} - 1\}$ for recurrence was selected as the optimal threshold. Probabilities of recurrence and death were estimated based on the combined SI(10%) and 3D-volume thresholds.

Cox regression was used to confirm the predictive significance of MRI-parameters for the time to recurrence and time to death outcomes. MRI-parameters were evaluated as continuous variables; CPF parameters were dichotomous. A two-sided α -level of .05 was used for the MRI-parameters. No adjustments for multiplicity were made because of the confirmatory one-sided nature of the tests.

RESULTS

Patient Characteristics

The distribution of stage, lymphnode involvement, histology, and treatment variables are presented in Table 1. Tumor characteristics were equally distributed with respect to treatment variables. Ten patients had FIGO stage IB₂ (bulky), 7 stage IIA, 26 stage IIB, 2 stage IIIA, 14 stage IIIB, and 3 stage IVA tumors. Median age at diagnosis was 53.3 (range, 29-75) years.

Individual MRI-Parameters

The overall results showed that low-DCE pattern, indicative of poor tumor perfusion and hypoxia, and high tumor volumes in the very early treatment phase (at 2-2.5 weeks of therapy), were associated with unfavorable therapy outcome, confirming the MRI-parameters identified in our exploratory study.²⁶ Among the DCE parameters, the heterogeneity-based SI(%) in the early treatment phase at 2-2.5 weeks of therapy, provided the best prediction of outcome. ROC analysis across the range of SI(%) showed that SI(10%) had the highest discriminating capacity (Fig. 2).

Univariate Cox regression showed that both SI(10%) and tumor volume significantly correlated with both time to recurrence and time to death. Lower SI(10%) and higher volume were associated with higher hazard ratios for recurrence ($P=.04$, $P=.03$, respectively) and death ($P=.03$, $P=.01$, respectively, (Table 2). SI(10%) and volume remained significant predictors in a 3-parameter model containing SI(10%), volume, and the combined CPFs for recurrence (HR=4.3 [1.3-15.1], $P=.02$; HR=2.7 [1.2-6.0], $P=.03$, respectively) and for death (HR= 2.6 [1.2-5.6], $P=.01$; HR=2.2 [1.3-3.7], $P=.003$, respectively). The correlation between SI(10%) and 3D-volume was .03, indicating minimal or no overlap in the information provided by each.

Sensitivity and Specificity of Parameters

Threshold values for SI(10%) and 3D-volume were explored. The thresholds to discriminate patients with favorable vs. unfavorable outcome were equivalent to the lowest SI(10%) and the highest 3D-volume values with no recurrence event. This corresponds to the goal of maximizing the sensitivity in predicting patients with unfavorable outcome, because these patients are the target group requiring change in therapy strategy to improve outcome. Based on this method, the discriminatory thresholds were 2.0 for SI(10%) and 22 cm³ for 3D-volume.

With these thresholds, the early-therapy SI(10%)<2.0 predicted recurrence and death with sensitivities of 100% and 79%, respectively (Table 3). The 3D-volume threshold of 22 cm³ predicted recurrence with same sensitivity but lower specificity than SI(10%), and death with higher sensitivity, but lower specificity (Table 3). The SI(10%) threshold of 2.0 in the current patient population was close to the threshold of 2.5 in our previous exploratory study.²⁶ When applied to our current patients, the prior threshold of 2.5 showed sensitivities similar to the 2.0 threshold, but inferior specificities for predicting recurrence and death (18%, 19%, respectively, Table 3/Note to Table). The mSI, averaging the SI values over the

entire tumor region without heterogeneity assessment, had lower specificities (33%, 33%) than the heterogeneity-based SI(10%) (56%, 58%) in predicting recurrence and death (Table 3).

Comparison of the 2-2.5-week Time Point with Pre-therapy MRI-Parameters

MRI-parameters at the early-therapy time point were compared to pre-therapy parameters using the Cox regression. Pre-therapy SI(10%) was not significantly associated with time to recurrence ($P=.06$) or death ($P=.08$). Pre-therapy tumor volume was associated with death ($P=.02$) but not recurrence ($P=.16$). In the sensitivity analysis, pre-therapy tumor volume was equivalent to early-therapy volume for the prediction of recurrence with a sensitivity of 100% and a relatively low specificity of 42% in both the pre- and early-therapy MRI. However, pre-therapy volume was inferior in predicting death with a sensitivity of only 79%, compared to 93% for the early-therapy volume. Similarly, the SI(10%) in early therapy showed better prediction. The sensitivities of the early-therapy SI(10%) in predicting recurrence and death were 100% and 79%, compared to 71% and 43% for the pre-therapy SI(10%).

Combined Heterogeneity-DCE and 3D-Volumetry Parameter (Combined MRI-Parameter)

The early-therapy MRI-parameters, SI(10%) and 3D-volume, were combined to derive a *combined MRI-parameter*. It improved the outcome prediction over that of the individual MRI-parameters alone, resulting in a sensitivity of 100% and specificity of 67% for predicting tumor recurrence; and a sensitivity of 93% and specificity of 48% for predicting death (Table 3).

For the *combined MRI-parameter*, the estimated probability of death was 53% in patients with both MRI-parameters beyond the thresholds (SI(10%)>2 and 3D-volume > 22 cm³), 13% with one parameter beyond thresholds, and 0% (upper confidence limit, 28%) with neither parameter beyond thresholds (Table 4a). The probability of recurrence for both MRI-parameters beyond thresholds was 37%. Kaplan-Meier estimate of actuarial 5-year local control rate (i.e. freedom from recurrence) was 58%, 100% and 100% for both, one and neither parameter beyond the threshold. Disease-specific and overall survival rates were 44%, 84%, 100%, and 44%, 81%, 90%, respectively.

Combined CPF/MRI Predictive Assay

The combination of all, the CPFs and the MRI-parameters was evaluated. For the individual CPFs (stage, lymphnode status and histology) sensitivities were 50% or less (Table 3). The combined CPFs were dichotomized into unfavorable (any one of: stage III-IV, involved lymphnodes, or non-squamous histology) vs. favorable (none of these) categories.

Sensitivity/specificity analysis showed that the combination of the MRI-parameters with CPFs further increased the discriminating capacity. The *CPF/MRI Predictive Assay* predicted all recurrences (sensitivity, 100%) and improved specificity to 71% over the *combined MRI-parameter* (67%) and combined CPF (51%) alone. It predicted cancer death with the same sensitivity as the combined MRI-parameter alone (93%), and improved the specificity to 60% over the combined MRI-parameter alone (48%) and combined CPF

(54%) alone (Table 3). Probabilities of recurrence and death were highest (42%, 67%) in patients with both unfavorable MRI-parameters and CPFs, and were 29% and 29%, respectively, with unfavorable MRI-parameters despite favorable CPFs (Table 4b).

DISCUSSION

Cervical cancer is a leading health problem world-wide. Standard chemo/radiation therapy fails in approximately one third of stage IB₂-IVA patients.^{29, 30} The classic prognostic factors, FIGO stage ¹, lymphnode status ² and histology ³, have been well established to guide therapy selection.³¹ However, they have been criticized as suboptimal in predicting outcome in the individual patient.^{4, 5} Specifically, the gold-standard CPFs have not accounted for heterogeneity of tumor responsiveness to the specific ongoing therapy, and have not been able to reliably predict failure early during the treatment course, when therapy adjustments are still feasible by radiation dose intensification, changes in the concurrent therapy, or addition of novel clinical trial therapies.

Our research was intended to develop an early predictive assay for ultimate outcome by augmenting essential information from both the established clinical *prognostic factors*, and from *predictive parameters* for the effectiveness of treatment. We took a new approach to investigate parameters that reflect the effective delivery of cytotoxic agents and oxygen to the heterogeneous tumor, and, once delivered to the tumor, assess the subtle early response to the specific treatment regimen. Our current study validates, with a different patient population and refined imaging methods, two independent MRI parameters as outcome predictors: the functional DCE parameter SI(10%), first discovered in our exploratory pilot study ²⁶, and the morphologic 3D-volume parameter. SI(10%), reflecting essential information on chemotherapy and oxygen delivery to the tumor, and residual 3D-volume, assessing early treatment response, predicted ultimate treatment outcome at an ultra-early time point, within 2-2.5 weeks of therapy start.

Functional MRI: Heterogeneity-based DCE Parameter SI(10%)

The DCE parameter SI(10%), which provides a heterogeneity-based quantification of poorly-perfused regions within the tumor, was confirmed as a sensitive independent predictor of recurrence and cancer death (Fig. 1, Tables 2-3). This finding is in keeping with our premise that the tumor perfusion status *during* therapy, which reflects the effectiveness of delivery of cytotoxic agents and oxygen to the tumor, critically influences the success of chemotherapy and RT. Poorly-perfused cell populations, represented by low-DCE regions within the heterogeneous tumor, likely contribute critically to treatment failure. In cervical cancer, there is ample indirect evidence that poor tumor blood supply adversely affects treatment response,^{14, 15, 17, 18} and that hypoxia-imparted radioresistance results in tumor recurrence and decreased survival.^{13, 16} Similarly, the effectiveness of chemotherapy delivery to the tumor critically depends on adequate tumor perfusion.^{9, 10} DCE-MRI, characterizes microvascular structure and function,^{32, 33} indirectly assesses perfusion and oxygenation status,^{20, 34, 35} correlates with microvessel density ²⁰ and with direct oxygen measurements ²² in cervical cancer.

SI(10%), as developed in our laboratory, specifically assessed the intra-tumoral heterogeneity of perfusion, a well-known phenomenon in solid tumors^{11, 12} that has been most challenging to assess in clinical patients. Our voxel-analysis identifies, separates and analyzes the heterogeneous low-perfusion (low-DCE) components within the tumor.¹¹ The clinical importance of heterogeneity assessment is shown by our result that SI(10%) was far superior in predicting treatment failure than the mean SI, averaging DCE over entire tumor region (Table 3).

Morphologic MRI: 3D-Volume, and Combined MRI-Parameter

While the functional parameter SI(10%) likely reflects oxygen and chemotherapy delivery to the tumor during therapy as a fundamental pre-condition for tumor cell kill by a specific cytotoxic regimen, the improved volume measurement by 3D-volumetry can now detect the actual early subtle response to the specific treatment in the individual patient. Irregular configurations and non-linear shrinkage of the individual tumor cannot be appreciated by the traditional uni- or bi-dimensional tumor measurements or physical examination. With the much better precision of MRI²³ and our measurement methodology, high residual 3D-volume, assessed in early therapy (2-2.5 weeks into treatment), independently predicted recurrence and death (Tables 2-3). By combining both, SI(10%) and 3D-volume, assessing the effective delivery and the early-therapy response measure of the cytotoxic effect, respectively, the accuracy of the ultra-early outcome prediction further improved over the individual MRI-parameters alone (Table 4a). Such a new combined MRI predictor has not been applied in clinical care for cervical cancer.

Comparison to the Exploratory Study

The present confirmatory study validates SI(10%) as a predictive parameter, and further refines the SI(10%) threshold. The threshold value of 2.0 in our current patient population separating favorable from unfavorable outcome, approximates the SI(10%) of 2.5 from our exploratory study.²⁶ The small difference between the current threshold and the pilot study is not unexpected, and may be in part related to the larger patient number and improved imaging technique of the current study population. However, the optimal threshold must be further refined through future study.

Combined MRI/CPF Predictive Assay

SI(10%) and 3D-volume were superior to CPFs in predicting outcome (Tables 2-3). This does not invalidate gold-standard CPFs, but opens opportunities to augment their prognostic abilities with the MRI-parameters. Our study explored this synergistic paradigm as a novel non-invasive *MRI/CPF Predictive Assay* by using the MRI predictors as adjunctive independent information. This further improved prediction of treatment failure to 100% and 93% sensitivity for recurrence and death. With the *MRI/CPF Predictive Assay*, probabilities of recurrence and death (42%, 67%) were highest in patients with both unfavorable CPFs and MRI-parameters, but were also substantial in those with unfavorable MRI-parameters despite favorable CPFs (29%, 29%, Table 4b). This suggests that unfavorable MRI parameters identified a high-risk subgroup within the favorable CPF category. Despite the

small size of the subgroups in this exploratory analysis, these trends provide direction for further study to validate the predictive assay and employ it clinically.

Although our study has the largest patient population and longest follow-up time of its kind to date, the confidence intervals of our results were wide. However, the high sensitivity of 93-100% in predicting unfavorable outcome suggests that the combined *CPF/MRI Predictive Assay* is a promising tool to effectively identify upfront most patients, who will ultimately fail therapy. In this regard, the sensitivity to predict treatment failure may be the most important criteria. With the poor salvage options after failed first-line therapy in cervical cancer, such timely prediction is critical. The early availability of the predictive assay within 2-2.5 weeks of therapy start can serve to further personalize treatment strategies. This may profoundly impact therapy success three-fold: First, early prediction of ultimate failure of ongoing standard therapy provides a window of opportunity to implement more intense treatment in those, whose high risk of failure justifies the toxicity of more aggressive therapy. Second, prediction of success may avoid unnecessarily intense or experimental therapies in patients with low risk of failure, thereby reducing morbidity and health care cost. Third, incorporation of such refined predictive assays into clinical trial designs can streamline patient selection and improve efficacy of studies investigating novel therapies.

Our results support that this novel non-invasive approach is achievable in a 45-minute MRI that can be implemented in community clinical settings to allow broad patient access.

In **conclusion**, our study confirmed the clinical feasibility and effectiveness of two independent MRI-parameters, quantifying heterogeneous tumor perfusion and early therapy-specific 3D-volume response, for predicting recurrence and death in cervical cancer. The combined predictive powers of the pre-treatment CPFs and the independent early-therapy MRI-parameters can be employed as a novel predictive assay for ultimate outcome of the specific ongoing treatment regimen, and may have profound impact to personalize therapy strategies in cervical cancer.

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Abbreviations

CPF	clinical prognostic factor
DCE	dynamic contrast-enhanced
HR	Hazard ratio
mSI	mean signal intensity
RT	radiation therapy
SI	signal intensity
SI(%)	lowest percentile of signal intensity of poorly perfused tumor voxels

SI(10%) lowest 10th percentile of signal intensity of poorly perfused tumor voxels
3D three-dimensional

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Figure 1.

A. High DCE at 2.5 weeks of chemo/radiation therapy

In this 52-year old woman with stage IIB squamous cell carcinoma of the cervix, MRI was obtained 2.5 weeks after RT start at a dose of 21.6 Gy in 12 fractions and 2 cycles of weekly Cisplatin chemotherapy. The volumetric MRI shows the cervical tumor region (arrows). The DCE MRI shows intense heterogeneous enhancement (arrows). The voxel histogram distribution of DCE demonstrates high and heterogeneous SI of the tumor and a high SI(10%) of 3.13. The patient is alive and well without primary tumor recurrence or metastasis 5 years and 2 months after therapy completion.

B. Low DCE at 2.5 weeks of chemo/radiation therapy

In this 42-year old woman with stage IIB adenocarcinoma of the cervix, MRI was obtained 2.5 weeks after RT start at a dose of 21.6 Gy in 12 fractions and 2 cycles of weekly Cisplatin chemotherapy. The volumetric MRI shows the cervical tumor region (arrows). The DCE MRI shows very low and heterogeneous enhancement (arrows). Voxel histogram distribution of DCE demonstrates overall much lower SI than in the patient in A. The SI(10%) is 1.70. This patient had primary tumor recurrence 1 month after therapy completion. Pelvic exenteration was attempted but the tumor was unresectable. She died of cervical cancer 12 months later.

Figure 2. ROC analysis of signal intensity percentiles

Receiver Operator Characteristic (ROC) analysis to determine the best signal intensity percentile (SI(%)) for the discrimination of recurrence (solid blue curve) and cancer death (dashed red curve). Area under the curve values of SI(2.5%) to SI(30%) are above 0.70, supporting the usefulness of the SI parameter across a range of percentiles associated with low DCE and indicative of poor perfusion and hypoxia. Consistent with the results of the exploratory study,²⁶ SI(10%) shows the best discriminating capacity.

Table 1

Patient Characteristics

Patient Characteristics	All Patients Percent (No.)	RT Dose		p *	RT Duration		Primary Recurrence [‡]		Disease-Spec. Survival [‡]	
		85 Gy	<85 Gy		<55 days	55 days	HR (CI)	p	HR (CI)	p
FIGO Stage										
I-II	69% (43)	9% (6)	60% (37)	.850	32% (20)	37% (23)	1.7 (0.4-7.6)	0.49	1.9 (0.6-5.4)	0.25
III-IV	31% (19)	5% (3)	26% (16)		13% (8)	18% (11)				
Lymphnodes										
Uninvolved	73% (45)	11% (7)	62% (38)	.705	31% (19)	42% (26)	2.3 (0.5-10.2)	0.28	3.2 (1.1-9.1)	0.03
Involved	27% (17)	3% (2)	24% (15)		14% (9)	13% (8)				
Histology										
Squamous	82% (51)	10% (6)	72% (45)	.185	37% (23)	45% (28)	4.0 (0.95-18.1)	0.07	4.9 (1.7-14.4)	0.004
Non-squamous	18% (11)	5% (3)	13% (8)		8% (5)	10% (6)				
Recurrence										
No	89% (55)	11% (7)	78% (48)	.262	34% (21)	55% (34)	—	—	—	—
Yes	11% (7)	3% (2)	8% (5)		11% (7)	0% (0)				
Cancer Death										
No	77% (48)	10% (6)	67% (42)	.404	30% (19)	47% (29)	—	—	—	—
Yes	23% (14)	5% (3)	18% (11)		15% (9)	8% (5)				
Overall Death										
No	74% (46)	10% (6)	64% (40)	.577	31% (19)	43% (27)	—	—	—	—
Yes	26% (16)	5% (3)	21% (13)		15% (9)	11% (7)				

Note: Numbers in parenthesis are patient numbers.

Treatment variables include RT dose and RT duration as important treatment -related factors influencing radiation therapy outcome. Statistical significance in the groups with treatment duration of <55 vs. 55 days is contrary to expectation, with less recurrences in the protracted treatment group.

* p value from Chi-square test.

[‡] Combined CPFs consists of stage (I-II vs. III-IV), lymphnode involvement (uninvolved vs. involved), histology (squamous vs. non-squamous). Unfavorable – any of: lymphnode involvement or stage III-IV or non-squamous histology. Favorable – none of these.

p value from Cox univariate analysis.

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Table 2
Univariate Hazard Ratio Estimates for Primary Tumor Recurrence and Cancer Death

Parameter	Primary Tumor Recurrence		Death of Cancer	
	Hazard Ratio(95%CI)	p-value	Hazard Ratio(95%CI)	p-value
SI(10%) ¹⁾	2.6 (1.0-6.5)	0.04	1.9 (1.0-3.5)	0.03
3D-Volume ²⁾	1.9 (1.1-3.5)	0.03	1.9 (1.2-2.9)	0.01
FIGO Stage ³⁾	1.7 (0.4-7.6)	0.49	1.9 (0.6-5.4)	0.25
Lymph Node Involvement ⁴⁾	2.3 (0.5-10.2)	0.28	3.2 (1.1-9.1)	0.03
Histology ⁵⁾	4.0 (0.9-18.1)	0.07	4.9 (1.7-14.4)	0.004

Note: Hazard ratio estimates and confidence intervals (CI) from univariate Cox regression models for time to primary tumor recurrence and time to cancer death:

¹⁾ For a decrease of one standard deviation (= decrease of 0.5);

²⁾ For an increase of one standard deviation (= increase of 24);

³⁾ Stage III-IVA vs. Stage I-II

⁴⁾ Yes vs. No

⁵⁾ Non-squamous vs. squamous

Table 3

Discriminating Capacity of MRI-Parameters, Combined CPF Parameter and Combined MRI/CPF Parameter to Predict Primary Tumor Recurrence and Cancer Death

Type of Parameters	Parameters	Primary Tumor Recurrence		Death of Cancer	
		Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
MRI	SI(10%) *	100 (59-100)	56 (42-70)	79 (49-95)	58 (43-72)
	mSI ¹⁾	100 (59-100)	33 (21-47)	86 (57-98)	33 (20-48)
	3D-Volume ²⁾	100 (59-100)	42 (29-56)	93 (66-100)	46 (31-61)
	Combined MRI Parameters ³⁾*	100 (59-100)	67 (53-79)	93 (66-100)	48 (33-63)
CPF	Stage ⁴⁾	43 (10-82)	71 (57-82)	43 (18-71)	73 (58-85)
	Lymphnode Status ⁵⁾	43 (10-82)	75 (61-85)	50 (23-77)	79 (65-90)
	Histology ⁶⁾	43 (10-82)	85 (73-94)	43 (18-71)	90 (77-97)
	Combined CPF Parameters ⁷⁾	71 (29-96)	51 (37-65)	79 (49-95)	54 (39-69)
Combined CPF/ Fct. MRI Assay	Combined MRI and Combined CPF ⁸⁾*	100 (59-100)	71 (57-82)	93 (66-100)	60 (45-74)

Note: Sensitivity and specificity estimates (in %) for comparing the discrimination of logistic regression models.

* The SI(10%) threshold of <2.0 vs. 2.0 was determined by ROC analysis in the current patient study population. The SI(10%) threshold of the independent patient population in the previous exploratory study²⁴ was 2.5. Using the threshold of 2.5, the sensitivities and specificities were 100% (59%-100%) and 18% (9%-31 %) for tumor recurrence, and 93% (66%-100%) and 19% (9%-33%) for death, respectively.

¹⁾ Mean SI (3.25 vs. >3.25)

²⁾ 3D-volume (22 cm³ vs. <22 cm³)

³⁾ Probability threshold from logistic regression model, based on both SI(10%) and 3D-volume

⁴⁾ FIGO Stage III-IV vs. stage I-II

⁵⁾ Lymphnodes involved vs. uninvolved

⁶⁾ Non-squamous cell (adeno- or undifferentiated carcinoma) vs. squamous cell carcinoma

⁷⁾ Unfavorable (defined as having any of: lymphnode involvement or stage III-IV or non-squamous histology) vs. Favorable (defined as having neither of these)

⁸⁾ Probability thresholds derived from logistic regression were identified separately for each CPF risk group, Unfavorable (any of: lymphnode involvement or stage III-IV or non-squamous histology) and Favorable (none of these).

Table 4
Combined MRI-Parameters: Estimated Probabilities (as %) of Primary Tumor Recurrence and Cancer Death

MRI	MRI-Parameter Description	Number of Patients	Primary Tumor Recurrence (%)	Death of Cancer(%)
Unfavorable ¹⁾	SI(10%) <2.0 and 3D-Volume < 22 cm ³	19	37 (16-62)	53 (29-76)
Intermediate ²⁾	SI(10%) <2.0 and 3D-Volume <22 cm ³ or SI(10%) ≥ 2.0 and 3D-Volume < 22 cm ³	32	0 *	13 (4 - 29)
Favorable ³⁾	SI(10%) ≥ 2.0 and 3D-Volume < 22 cm ³	11	0 *	0 (0 - 28)

Note:

1-3)Details are presented in column "MRI-Parameter Description". 95% CI in parenthesis.

* The probability of recurrence in patients with at least one MRI parameter beyond threshold is 0% by definition because of the selection of thresholds to produce 100% sensitivity for recurrence.

¹⁾Unfavorable = both MRI-parameters beyond threshold

²⁾Intermediate = one beyond threshold

³⁾Favorable = none beyond threshold.

Table 5
Combined MRI and CPF Parameters (CPF/MRI Predictive Assay): Estimated Probabilities (as %) of Primary Tumor Recurrence and Cancer Death

CPF MRI	Primary Tumor Recurrence (%)		Death of Cancer(%)	
	Unfavorable	Favorable	Unfavorable	Favorable
Unfavorable ¹⁾	42 ⁴⁾	29 ⁵⁾	67 ⁶⁾	29 ⁵⁾
Intermediate ²⁾	0 *	0 *	17 ⁷⁾	7 ⁸⁾
Favorable ³⁾	0 *	0 *	0 ⁹⁾	0 ¹⁰⁾

Note: 1-3) Parameter description as stated in Table 4a.

⁴⁾95% CI: 15-72

⁵⁾CI: 4-71

⁶⁾CI: 35-90

⁷⁾CI: 4-41

⁸⁾CI: 0-34

⁹⁾CI: 0-71

¹⁰⁾CI: 0-37.

* The probability of recurrence in patients with only one MRI parameter beyond threshold is 0% by definition because of the selection of thresholds to produce 100% sensitivity for recurrence.