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Translating Response During Therapy into Ultimate Treatment Outcome: A Personalized 4-Dimensional MRI Tumor Volumetric Regression Approach in Cervical Cancer

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Abstract

Purpose—To assess individual 3-dimensional volumetric tumor regression pattern in cervical cancer during therapy using serial 4-dimensional MRI and define the regression parameters' prognostic value validated with local control and survival correlation.

Methods and Materials—One hundred and fifteen patients with stages IB₂–IVA cervical cancer treated with radiation therapy (RT), underwent serial MRI before (MRI 1) and during RT, at 2–2.5 weeks (MRI 2, at 20–22 Gy), and at 4–5 weeks (MRI 3, at 45–50 Gy). Eighty patients had a 4th MRI 1–2 months post-RT. Mean follow up was 5.3 years. Tumor volume was measured by MRI-based 3-dimensional volumetry, and plotted as dose(time)/volume regression curves. Volume regression parameters were correlated with local control, disease-specific and overall survival.

Results—Residual tumor volume, slope and area under the regression curve correlated significantly with local control and survival. Residual volumes $\geq 20\%$ at 45–50 Gy were independently associated with inferior 5-year local control (53% vs. 97%, $p < 0.001$) and disease-specific survival rates (50% vs. 72%, $p = 0.009$) than smaller volumes. Patients with post-RT residual volumes $\geq 10\%$ had 0% local control and 17% disease-specific survival, compared to 91% and 72% for $< 10\%$ volume ($p < 0.001$).

Conclusion—Using more accurate 4-dimensional volumetric regression analysis, tumor response can now be directly translated into individual patients' outcome for clinical utilization. Our results define two temporal thresholds critically influencing local control and survival. In patients with $\geq 20\%$ residual volume at 45–50 Gy and $\geq 10\%$ post-RT, the risk for local failure and death are so high that aggressive intervention may be warranted.

Keywords

Cervical cancer; Tumor volume; Tumor volume regression; Magnetic resonance imaging

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INTRODUCTION

Despite advances in the therapy approach, the treatment of advanced cervical cancer remains a challenge, and approximately one third of patients with stage IB₂-IVA tumors die of the disease (1). Once tumor recurrence is found after definitive radiation (RT) and chemotherapy, salvage options and outlook are poor (2).

Early response assessment during the treatment course, while adjustments in therapy can still be made, has been a challenge because of the difficulty in accurately measuring tumor volume, irregular shapes and non-linear tumor shrinkage during treatment. Evaluation of tumor response and therapy success have generally relied on clinical palpation of the tumor by pelvic examination. However, clinical palpation is known to be relatively insensitive in accurately assessing tumor size and volume – particularly *during* the ongoing course of RT (3–5).

Magnetic resonance imaging (MRI) provides highly precise assessment of tumor volume and extent in cervical cancer, compared to clinical palpation and other imaging modalities (6–8). Three-dimensional (3D) MRI-based volumetry is established as the most accurate tumor measurement in cervical cancer based on histopathologic volume correlation (9). Because MRI is non-invasive and can be performed serially during RT and after treatment (10,11), such high-precision tumor measurement can encounter the challenges of irregular shape and non-linear tumor shrinkage and improve accuracy for subtle volume changes. This serial quantitative volumetry provides a new “glimpse” into the “*4th dimension of tumor volume*”: the longitudinal volumetric tumor changes during and after the course of RT in cervical cancer.

Tumor response assessments are commonly performed in daily practice and for clinical trials. However, response alone does not readily translate into the reality of ultimate therapy outcome with respect to local control and survival. Even with quantitative response measurements, using one- or two-dimensional measurements, size criteria with prognostic value for local control and survival have not been clearly defined in cervical cancer. In the limited experience with studies of serial MRI during RT, the timing of imaging has been variable, and correlation with ultimate tumor control is sparse (12,13). Therefore, the significance of MRI-based longitudinal tumor volume change during RT is unclear, and there are no well-defined response criteria that judge true therapy responsiveness and can be employed in clinical practice to optimize the therapy strategy.

The purpose of this study was to define and validate 4-dimensional volumetric tumor regression parameters in cervical cancer that are significant for ultimate therapy outcome and potentially applicable to adapt therapy strategy.

The specific aims were: (1) to measure 3D tumor volume with MRI before, during and after the RT course; (2) to develop dose – tumor volume regression curves and assess velocity of tumor shrinkage, and (3) to derive volume regression parameters and evaluate their correlation with local tumor control, disease-specific and overall survival.

METHODS AND MATERIALS

Patient population and treatment

One hundred and fifteen patients with biopsy-proven advanced cervical cancer, who were treated with RT, were studied prospectively with serial MRI. Sixty-five patients had had FIGO stage IB₂-II, and 50 had stage III-IV disease. Median age at diagnosis was 50 (range: 25–89) years. Detailed patient characteristics are presented in Table 1.

Pre-treatment evaluations were performed following FIGO guidelines (14), and included history and physical examination, complete blood count and blood chemistries, CT of the abdomen and pelvis, chest radiography; and chest CT, cystoscopy and proctoscopy, if clinically indicated.

Patients were treated at the Universities of Iowa and Oklahoma from 1993 to 2004. Radiation therapy consisted of standard external beam RT using 6–24 MV photons to a dose of 39.6–50.4 Gy (mean: 47.2) in 1.8–2.0 Gy fractions to the pelvis. In all but 5 patients, the external radiation was combined with brachytherapy, using low-dose-rate intracavitary brachytherapy in 96, low-dose-rate interstitial brachytherapy in 6, and high-dose-rate brachytherapy in 8 patients. In patients, who did not receive brachytherapy, for medical or tumor-related reasons, additional reduced-field external beam RT was given to the central pelvic tumor. Concurrent weekly Cisplatin-based CT was given in 52 patients.

MRI and image analysis

The serial MRI examinations were obtained on an IRB approved protocol: MRI 1 at the therapy start; MRI 2 during RT at 2–2.5 weeks of RT, corresponding to a cumulative dose of 20–22 Gy; MRI 3 at 4–5 weeks of RT, at a dose of 45–50 Gy. Eighty of the 115 patients also had a fourth MRI at 1–2 months after completion of RT.

The serial MRI examinations were obtained on a 1.5-T scanner with a body coil. Imaging included sagittal T₂-weighted images (TR=4000–5600 ms, TE=100–120 ms, FOV=30–40 cm, matrix=256 × 192–256, slice thickness=4 mm, gap=1 mm, NEX=2; Fig. 1 and Fig. 2), axial T₂-weighted and axial T₁-weighted images (TR=350–700, TE=5–17, FOV=30–40, matrix=256 × 192–256, slice thickness=7 mm, slice gap=1 mm, NEX=2–4).

For the tumor volume measurement, 3D-volumetry was employed for each serial MRI as described in detail earlier (11). The tumor region was identified on the sagittal T₂-weighted images and contoured. Volumes were computed by multiplication with the slice profile, using software developed in our laboratory.

Proportional volume was defined as 100% for MRI 1 at RT start. For subsequent measurement time points at MRI 2 (20–22 Gy), MRI 3 (45–50 Gy), and post-therapy MRI 4, proportional volume was defined as the percentage of residual tumor volume at the measurement time point, divided by the volume in MRI 1. The temporal changes of tumor volume were quantified by plotting regression curves of the proportional tumor volume at the dose levels of MRI 1, MRI 2 and MRI 3. The slope (%/Gy), representing the velocity of tumor shrinkage during RT, and the area under the curve (AUC, in %) of the graph plotting the proportional volume over time, were calculated from each patient's regression curve.

The proportional volumes at the specific RT dose levels of 20–22 Gy, 45–50 Gy, and at the post-RT MRI were assessed separately with respect to the outcome endpoints. Optimal thresholds of proportional volumes at these time points, and of slope and AUC were determined by Receiver-Operating-Characteristic (ROC) analysis.

Follow-up and outcome correlations

Patients were evaluated post-therapy in 3- to 6-monthly intervals for at least 5 years, and yearly thereafter. Mean follow up was 5.3 (range: 0.2–9.4) years. *Local recurrence* was defined as tumor re-growth or persistence in the cervix or uterus after therapy completion, *death of disease* as death from cervical cancer or cancer complications. MRI parameters were correlated with outcome endpoints. The parameters were subjected to multivariate analysis using the Cox proportional hazard model. Kaplan-Meier analysis was employed to estimate actuarial local

control, disease-specific and overall survival rates. Differences among patient groups were estimated with the log-rank test.

RESULTS

In the 115 patients, the regression slopes derived from the plots of the proportional tumor volumes at MRI 2 and MRI 3 during RT showed wide variability among patients, ranging from 0.3–3.6 %/Gy (mean:1.8, median:1.8, SD:0.5). Similarly, AUCs were highly variable, ranging from 11.3–49.8 % (mean:26.1, median:25.2, SD:7.2). There was no significant difference in slope or AUC between patients receiving chemotherapy vs. those with RT alone, nor between patients with squamous vs. non-squamous cell carcinomas.

Both regression slope and AUC correlated with local tumor control (Fig. 3). Local control increased progressively with increasingly steep slopes, reaching above 85% for slopes beyond 2%/Gy and declining below 45% with slopes below 1%/Gy (Fig. 3a). The AUC of the proportional volume correlated inversely with local control. Local control decreased progressively with increasing AUC, falling to below 60% for AUCs above 35%, and increasing to above 90% for AUCs below 20% (Fig. 3b). Similarly, increasingly steep slopes were associated with increasing disease-specific and overall survival (Fig. 4a and Fig. 5a). AUC correlated inversely with disease-specific survival and overall survival (Fig. 5b and 5b). Slopes of ≤ 1.7 %/Gy correlated with significantly inferior 5-year local control (54% vs. 90%, $p < 0.001$), disease-specific survival (50% vs. 68%, $p = 0.039$) and overall survival rates (44% vs. 63%, $p = 0.032$) than higher slopes. Similarly, AUCs of $> 27.5\%$ were associated with significantly inferior local control (55% vs. 90%, $p < 0.001$), disease-specific survival (48% vs. 70%, $p = 0.019$) and overall survival rates (39% vs. 63%, $p = 0.008$) than lower AUCs.

In the analysis by specific measurement time points, volume regression at 45–50 Gy/4–5 weeks and at 1–2 months post-RT showed the strongest correlation with outcome. Proportional tumor volumes of $\geq 20\%$ at 45–50 Gy correlated with significantly inferior 5-year local control (53% vs. 97%, $p < 0.001$), disease-specific survival (50% vs. 72%, $p = 0.009$) and overall survival rates (47% vs. 64%, $p = 0.037$) than smaller proportional volumes (Fig. 6). Volume regression at 20–22 Gy/2–2.5 weeks showed a smaller, but significant difference for local control, but not for disease-specific and overall survival ($p = 0.007$, 0.08, and 0.07, respectively).

In the patients with a fourth MRI 1–2 months after RT completion, strong outcome correlation for MRI 4 was observed. If the proportional tumor volume post-RT was $\geq 10\%$, none of the patients attained local control, and 5-year disease-specific and overall survival rates of 17% were poor, compared to 91% local control ($p < 0.001$), 72% disease-specific survival ($p < 0.001$) and 62% overall survival ($p = 0.001$) in patients with $< 10\%$ proportional volume (Fig. 7).

The disease-specific survival of 17% despite the 0% local control in the group with $\geq 10\%$ post-RT volume, was related to two long-term survivors within this group. In both, pelvic recurrence was successfully salvaged with exenteration because their recurrences were diagnosed *early* through increased surveillance prompted by slow regression in MRI 3 and persistent tumor in MRI 4. In a 57-year old woman with Stage IIB adenocarcinoma, persistent tumor 1 month post-RT on MRI 4 (proportional volume: 44%) prompted close follow up. No intervention was undertaken 1 month post-RT, because of the uncertainty of significance of the MRI findings at that time. Continued clinical follow-up showed no visible or palpable tumor. When repeat MRI 3 months post-RT again showed persistent tumor, cervical biopsy was performed and showed adenocarcinoma. Anterior exenteration showed adenocarcinoma with parametrial extension, perineural invasion, and uninvolved lymph nodes. The patient is alive and well 9.4 years post-therapy. In the second patient, a 49-year old woman with stage IIIB squamous cell carcinoma of the cervix, slow volume regression was observed on MRI 3. The proportional

volume at MRI 4 was 42%. Anterior exenteration showed squamous cell carcinoma involving vagina and cervix. Lymph nodes were uninvolved. The patient is alive and well 8.3 years post-therapy.

When analysis of outcome endpoints was stratified according to stage (I-II vs. III-IV), lymph node status (uninvolved vs. involved), differences in local control rate, based on the proportional volume at 45–50 Gy, remained statistically significant (Table 2). Differences in disease-specific and overall survival rate remained significant in the subgroups with stage III-IV and uninvolved lymph nodes. Outcome differences based on proportional volume at 20–22 Gy retained statistical significance only for local control, not for survival. Differences in outcome based on MRI 4 remained highly significant in all subgroups, except for overall survival in the stage I-II subgroup (Table 3). Differences based on slope and AUC also remained significant for local control in all but stage I-II subgroups; and for disease-specific and overall survival in stage III-IV and uninvolved lymph node subgroups, except for slope, which lost significance in both lymph node subgroups.

In the multivariate model incorporating proportional volume at 45–50 Gy, clinical tumor size, stage (III-IV vs. I-II), and lymph node status (involved vs. uninvolved), the proportional volume and clinical tumor size independently correlated with local control. Proportional volume and stage correlated with disease-specific survival, and only stage with overall survival. For the post-RT measurement (MRI 4), the proportional volume and clinical tumor size correlated with local control. Only proportional volume correlated with disease-specific and overall survival. For the early-RT measurement at 20–22 Gy (MRI 2), proportional volume did not show independent correlation with any of the outcome endpoints.

DISCUSSION

The critical influence of tumor volume on treatment outcome in cervical cancer is well established. Both local control and survival can profoundly change within the same stage based on tumor size (15,16). MRI is now increasingly used in cervical cancer (6–8,17–20) and has greatly refined our ability to delineate and measure cervical tumors (9) over the semi-qualitative approach and inaccuracies of clinical palpation (3–5). Tumor measurement is no longer limited to uni- or bi-dimensional diameters assuming ellipsoid tumor shapes. It is well recognized that cervical tumors are not ellipsoid but highly irregular and shrink in non-linear fashion during RT. The ability to accurately measure complex configurations and differentiate radiation fibrosis from tumor (10,21,22) make MRI the optimal method to non-invasively assess tumor volume serially, not only before but also during the course of RT.

High-precision serial volumetry provides new insights into the individual patients' tumor regression dynamics during ongoing RT. If criteria of tumor regression can be established that are relevant for ultimate therapy outcome, *and* can be detected early enough, while the RT course is still ongoing, timely and individualized adaptations of the treatment regimen become realistic, including RT dose intensification, changes in the concurrent therapy regimen, or addition of novel clinical trial therapies.

However, despite the increasing utilization of MRI in cervical cancer, most clinical use has remained limited to pre-therapy assessments (17–20,23), or after the completion of therapy (10). With only sparse data in the literature on imaging-based tumor regression during RT (11–13), and its uncertain clinical significance, this quantitative information has not been widely used with clear guidelines.

Our data provide clinical translation of 4-dimensional volumetry in cervical cancer, and show that the volume regression profoundly influences local control and survival. The observed correlation between slope, representing velocity of tumor shrinkage and clearance during RT,

and local control suggests that slope is an indirect measure of the radio-responsiveness of the local tumor in the individual patient (Fig. 3a). Similarly, the inverse correlation between AUC, likely representing residual tumor bulk persisting during RT, and local control suggests that AUC reflects inherent radio-resistance (Fig. 3b). In addition to local control, slope and AUC also translated into disease-specific and overall survival (Fig. 4 and Fig. 5). The outcome correlations of slope, AUC and proportional volumes at MRI 3 and MRI 4 (Fig. 6 and Fig. 7) suggest that these parameters can be applied as classifiers for individual patients' risk of local recurrence and death of disease.

The weaker outcome correlation of MRI 2, that was limited to local recurrence, may be explained by inaccuracies of morphologic imaging in reflecting actual tumor cell kill within the first 2 weeks of RT. MRI-detectable morphologic volume response may lag behind the actual cell death during this very early treatment phase.

Since our original work in 1996 (11), first evaluating serial MRI-based 3D volume regression during RT, a study of 42 patients by Hatano *et al.* (12) has correlated serial MRI-based tumor volume with local control. Using diameter-based ellipsoid computations pre-RT, post-RT MRI and a single measurement at a dose of 30 Gy, regression to <30% at 30 Gy correlated with local control, but no information on survival is available. These findings are in agreement with the favorable local control seen with fast regression in our larger and longer-term study. Ohara *et al.* (13) studied 12 patients by ellipsoid volume pre-RT and at variable times 18–34 days after RT start, and found correlations of regression slope with tumor response at RT completion.

Our study lacks histologic validation of the MRI findings as performed by Hatano *et al.* (12) and Vincens *et al.* (24), which show conflicting correlations of residual tumor based on MRI vs. histology. Ultimately, no imaging test can achieve 100% accuracy, and residual tumor remains challenging to assess during/after RT (24). However, we believe that the long-term patient outcome (local control, survival) may be a more important endpoint to validate the clinical usefulness of MRI than histology.

For the clinical applicability of the 4-dimensional volumetry information, a central question remains: *What is the optimal time point of tumor measurement*, that provides best prediction of local control and survival, and at the same time is practically feasible and available early enough during therapy to enable risk-adapted treatment approaches? Our results clearly define two key temporal threshold parameters, proportional volume of 20% at MRI 3 and of 10% at MRI 4, which have profound impact on therapy outcome and can be potentially implemented to individualize and optimize therapy.

For tumor regression, the MRI 3 at 45–50 Gy was the most sensitive measurement time point during RT that independently correlated with local control and survival. In patients with proportional volumes of <20% at 45–50 Gy, standard-of-care therapy had a high probability of success, with 97% 5-year local control rate (Fig. 6). With slower regression, ($\geq 20\%$), outcome was significantly worse, with 53% local control and 47% survival. These results suggest that, at a minimum, more intense monitoring with repeat MRI is indicated in the high-risk group with $\geq 20\%$ residual volume at 45–50 Gy.

The repeat MRI at 1–2 months identified the poorest outcome group. Our observation that local control appears not achievable (Fig. 7) without aggressive surgical intervention in patients with a post-RT tumor volumes of $\geq 10\%$, suggests that work-up to determine recurrence should be undertaken, even if clinical findings are unsuspecting. The early discovery of local recurrence in our two patients with $\geq 10\%$ residual tumor, was prompted tumor persistence of $>10\%$ on MRI 4 in the absence of suspicious clinical findings. Early intervention by radical exenteration impacted the ultimate outcome and accounted for the 17% survival rate despite the 0% local control rate (Fig. 7).

Based on our data, a practical algorithm for clinical decision-making may be proposed for the use of 4-dimensional volumetry imaging during ongoing RT in cervical cancer. This includes 3D tumor measurement from a pre-RT MRI, which is now frequently used routinely for conventional staging work-up and RT planning. The pre-therapy MRI is followed by an MRI at 45–50 Gy, which is also now increasingly employed before or during brachytherapy (25). If proportional tumor volume at 45–50 Gy is favorable (<20%), local control is expected to be high (97%) and no change in loco-regional therapy would be required.

However, if $\geq 20\%$ volume persists at 45–50 Gy, a post-therapy MRI should be obtained 1–2 months after RT. This early post-RT time point represents a critical time window for radical exenteration, before further tumor progression to pelvic wall structures, lymph nodes or distant sites preclude this salvage option. In patients with $\geq 10\%$ volume 1–2 months post-therapy, aggressive surveillance including clinical examination, repeat MRI, molecular imaging with PET/CT (26), post-RT tumor biopsies, and consideration of radical resection as the intervention with a potential of cure, may be warranted.

Beyond this algorithm, a better understanding of the impact of individual volumetric regression patterns *during* RT on ultimate local control and survival in the individual patient may be useful to adapt the treatment *much earlier*, while the RT course is still ongoing. In patients with slow regression, evidenced by $\geq 20\%$ of persistent tumor at 4–5 weeks of RT, perhaps outcome can be influenced by RT dose intensification, including choice and timing of brachytherapy, image-guided brachytherapy approaches to more effectively treat larger residual tumor volumes (25), or by the use of experimental novel concurrent therapy regimens. The concepts of both, adaptive surveillance and intratreatment adjustments of therapy, deserve further study.

CONCLUSION

MRI-based 4-dimensional volumetric tumor regression pattern reflects the inherent radioresponsiveness of cervical cancers. The temporal threshold criteria of proportional tumor at 45–50 Gy and 1–2 months post-therapy independently correlate with local control and survival, and may be useful for the adaptation of treatment within the time frame of the RT course or shortly thereafter.

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Conflicts of Interest Notification

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Fig. 1. Serial MRI in cervical cancer – rapidresponse, high slope and low AUC

Serial MRI in a 41-year-old woman with a 7 cm stage IIB squamous cell carcinoma of the cervix. **(A)** Sagittal T2-weighted image of MRI 1 shows a well-circumscribed tumor (arrows) in the cervix. **(B)** MRI 2 at a cumulative dose of 19.8 Gy in 11 fractions/2 weeks shows tumor regression to a proportional volume of 89%. **(C)** In MRI 3 at 43.2 Gy in 24 fractions/5 weeks, the proportional volume is 4%. **(D)** The slope of tumor regression is 2.2 %/Gy and the AUC is 24 %. The patient is alive and well 6 years and 11 months after therapy.

(A) MRI 1 **(B) MRI 2** **(C) MRI 3** **(D) MRI 4** **Fig. 2. Serial MRI in cervical cancer – slow response, low slope and high AUC**

Serial MRI in a 40-year-old woman with a 7 cm stage IIIB squamous cell carcinoma of the cervix with uninvolved lymph nodes. **(A)** Sagittal T2-weighted image of MRI 1 shows the tumor (arrows) in the cervix. **(B)** At the time of MRI 2 at a dose of 21.6 Gy in 12 fractions, the proportional tumor volume is 87%, similar to the patient in Fig. 1. **(C)** However, at MRI 3 at 45 Gy in 25 fractions, the regression is much slower, and the proportional volume is still 40%. **(D)** The tumor regression slope is 0.8 %/Gy and the AUC is 50%. The post-RT proportional volume 1 month after RT completion is still 31%. The patient had tumor recurrence 1 year and 3 months after therapy completion and died 11 months later.

Fig. 3. Correlation of regression slope and AUC with local control

Percentage of patients with local control is plotted as a function of regression slope (A) and AUC (B) at dose levels of MRI 1, MRI 2, MRI 3. Local control progressively increases with increasing slope, indicative of the velocity of tumor shrinkage during RT. Local control progressively decreases with increasing AUC, indicative of integral residual proportional tumor volume over time throughout the course of RT (curve fitting with Piecewise Cubic Hermite Interpolating Polynomial [PCHIP]).

Fig. 4. Correlation of regression slope and AUC with disease-specific survival

Percentage of patients alive and without disease as a function of regression slope (A) and AUC (B) at dose levels of MRI 1, MRI 2, MRI 3. The percentage of patients alive and without disease progressively increases with increasing slope, and decreases with increasing AUC (curve fitting with PCHIP).

Fig. 5. Correlation of regression slope and AUC with overall survival

(A) Percentage of patients alive is plotted as a function of regression slope and AUC (B) at dose levels of MRI 1, MRI 2, MRI 3. The percentage of patients alive progressively increases with increasing slope, and decreases with increasing AUC (curve fitting with PCHIP).

Fig. 6. Kaplan-Meier analysis of local control, disease-specific and overall survival as a function of proportional tumor regression at 45–50 Gy (MRI 3)

Local control, disease-specific and overall survival are significantly higher in the patient group with rapidly regressing tumors with proportional tumor volumes of $<20\%$ at 45–50 Gy (solid line), compared to slowly regressing tumors with volumes of $\geq 20\%$ (dotted line) ($p < 0.001$, $p = 0.009$, and $p = 0.037$, respectively, log-rank test).

Fig. 7. Kaplan-Meier analysis of local control, disease-specific and overall survival as a function of proportional tumor regression at 1–2 months post-RT (MRI 4)

Local control, disease-specific and overall survival are significantly higher in the group with rapidly regressing tumors with proportional tumor volumes of <10% at 1–2 months post-RT (solid line), compared to volumes of ≥10% (dotted line) ($p < 0.001$ for all, logrank test).

Table 1

Patient characteristics.

Patient Characteristics	Patient Number	Percentage
Age		
<45	31	27%
≥45	84	73%
Stage		
I	21	18%
II	44	38%
III	37	32%
IV ^{a)}	13	11%
Lymph Nodes		
Uninvolved	82	71%
Involved	33	29%
Histology		
Squamous	96	83%
Non-Squamous	19	17%

^{a)} **Note:** Includes one patient with stage IVB disease, metastasis to inguinal lymph node.

Table 2

Five-year actuarial rates of local control, disease-specific survival and overall survival for proportional tumor volume at 45–50 Gy: stratified by stage and lymph node status.

Parameter MRI 3 (45–50 Gy)	Local Control			Disease-Specific Survival			Overall Survival		
	< 20%	≥20%	p	<20%	≥20%	p	<20%	≥20%	p
Stage I-II III-IV	95%	80%	0.045	79%	74%	0.623	65%	71%	0.600
	100%	30%	<0.001	61%	27%	0.008	61%	24%	0.002
Lymph nodes Uninvolved Involved	98%	53%	<0.001	82%	53%	0.007	72%	48%	0.023
	92%	55%	0.02	39%	44%	0.678	36%	44%	0.837

Note: Rates computed by Kaplan Meier analysis, differences between groups estimated with log-rank test. Significant p-values printed in bold.

Table 3

Five-year actuarial rates of local control, disease-specific survival and overall survival for proportional tumor volume at 1–2 months post-RT: stratified by stage, lymph node involvement and histology.

Parameter MRI 4 (post-RT)	Local Control			Disease-Specific Survival			Overall Survival		
	<10%	≥10%	p	<10%	≥10%	p	<10%	≥10%	p
Stage I-II III-IV	95%	0%	<0.001	83%	33%	0.008	71%	33%	0.147
	86%	0%	<0.001	58%	11%	0.006	55%	11%	0.016
Lymph nodes Uninvolved Involved	92%	0%	<0.001	79%	25%	<0.001	70%	25%	0.019
	86%	0%	<0.001	48%	0%	0.006	44%	0%	0.010

Note: Rates computed by Kaplan Meier analysis, differences between groups estimated with log-rank test. Significant p-values printed in bold.