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Assessment of parametrial invasion of cervical carcinoma, the role of T2-weighted MRI and diffusion weighted imaging with or without fusion

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AIM: To evaluate the diagnostic performance of diffusion-weighted imaging (DWI), with and without fusion images, in addition to regular T2-weighted (T2W) sequences for assessment of parametrial invasion.

MATERIALS AND METHODS: This prospective cohort included cervical cancer patients who underwent preoperative magnetic resonance imaging (MRI) with T2W and axial DWI sequences prior to radical hysterectomy. Retrospectively, two radiologists independently and blindly scored the likelihood of parametrial invasion by means of a six-point confidence scale. Parametrial invasion was determined by surgical–pathological results. Performance indices for diagnostic tests and area under the receiver operating characteristic curve (AUC) analyses were performed. *P*-Values of <0.05 were considered statistical significant. Ethical board approval was obtained.

RESULTS: Of 65 included patients, parametrial invasion was found in eight patients. A statistically significant increase in diagnostic performance for the assessment of parametrial invasion was found when T2W MRI was fused with DWI (fusion T2W/DWI), especially decreasing false-positive findings: the positive predictive value of parametrial invasion using T2W MRI versus fusion T2W MRI/DWI increased from 29% to 50% for observer 1 and from 23% to 50% for observer 2 (AUC=0.80–0.67 versus 0.94–0.94).

CONCLUSIONS: Fusion T2W MRI/DWI shows a significant increase in diagnostic performance for the assessment of parametrial invasion in early-stage cervical carcinoma.

Introduction

Staging of cervical cancer is performed by clinical examination.[1] The 2014 International Federation of Gynecology and Obstetrics (FIGO) stage of cervical cancer is one of

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the most important factors in determining treatment options. Parametrial invasion is the discriminating factor between FIGO stage IB and IIB disease. FIGO stage IB disease is commonly treated with radical hysterectomy and pelvic lymphadenectomy whereas stage IIB disease is being treated with chemo-radiation.[2] When parametrial invasion, lymph node metastases, or a combination of other prognostic unfavourable risk factors are recognised on histopathological examination after surgery, adjuvant chemo-radiation is advised.[3] Radiation therapy following a radical hysterectomy is associated with higher morbidity and an increase in costs.[3,4] Therefore, adequate preoperative staging is considered essential.[5]

Multiple research groups have evaluated the predictive value of magnetic resonance imaging (MRI) for parametrial invasion, a systematic review showed MRI to be superior to clinical examination.[6] Recently, the European Society of Gynaecological Oncology (ESGO) incorporated pelvic T2-weighted (W) MRI as a mandatory work-up tool for cervical cancer staging.[7] Nevertheless, evaluation of parametrial invasion on conventional T2W imaging proves to be difficult, as 13–25% of parametrial invasion is being missed.[6,8]

On MRI, exclusion of parametrial invasion is most often defined by a regular hypointense cervical stromal ring, without signs of disruption.[9,10] Due to tumour growth, pressure, oedema, and the biological reaction of the surrounding cervical tissue, assessing parametrial invasion on T2W MRI is prone to false-positive results as the hypointense ring is broken by non-tumorous tissue.[11,12] Diffusion-weighted magnetic resonance imaging (DWI) bears the potential to overcome this problem. DWI reflects cell density by measuring water diffusion. Malignant cervical tissue has a higher cell density compared to normal cervical stroma or parametrium. Peri-tumoural oedema does not show diffusion restriction, which makes it possible to make the differentiation between peri-tumoural oedema and tumour.[13]

Studies focusing on DWI for the prediction of parametrial invasion are scarce. The potential increase in diagnostic performance of DWI for the evaluation of parametrial invasion has been highlighted in two retrospective single institution trials.[14,15] One study showed some additional benefit of fusion images (T2W fused with DWI).[14] Two prospective cohort studies could not draw firm conclusions as only a small part of their study populations (20 and 25 patients) had DWI sequences available for the interpretation of parametrial invasion.[16,17]

This study aims to evaluate the diagnostic performance of DWI in addition to T2W MRI sequences for assessment of parametrial invasion. In addition, the additional benefit of fusion images (T2W fused with DWI) was evaluated in this perspective.

Materials and methods

Patients

From a prospective cohort of patients with histologically proven primary cervical cancer, all the patients between April 2011 and June 2016 planned for radical hysterectomy with pelvic lymphadenectomy were selected (Fig 1). The standard diagnostic work-up of patients with early-stage disease consisted of a gynaecological examination under general anaesthesia, chest radiography, and MRI of the pelvis. All patients were discussed in a multidisciplinary team meeting consisting of a nuclear physician, radiologist, pathologist, gynaecological oncologists, medical oncologist, and radiation oncologist. To prevent unnecessary adjuvant treatments and reflect current daily practice, a strict policy for allocation of patients to surgery was advocated; patients with clear or highly suspected parametrial invasion (FIGO IIB) were allocated to chemoradiation. Ethical approval was given and informed consent for the use of (coded) images was waived by the local ethical committee, as the data were analysed anonymously in accordance with the Institutional Review Board guidelines (no. 16-4-023).

MRI

MRI was performed within 8 weeks prior to surgery. All examinations were undertaken on an Intera Achieva; Philips Medical Systems, Best, The Netherlands; or Siemens Magnetom Avanto/Biograph mMR PET-MR, Siemens Healthineers, Erlangen, Germany.

The majority of the MRI examinations (54%, n=35) were performed using a 1.5 T MRI unit with a phased-array surface coil. Patients were placed in a feet-first supine position. The imaging protocol comprised standard two-dimensional (T2W) fast spin-echo images in three orthogonal directions. The axial and coronal images were angled perpendicular and parallel to the cervical axis, respectively. The remaining MRI examinations (46%; n=30) were performed using a 3 T MRI unit using a similar T2W protocol. For axial DWI, a single-shot echo-planar protocol was performed with b=0 as the lowest and b=800 (n=5) or b1000 (n=60) as the highest b-value. Apparent diffusion coefficient (ADC) maps were automatically generated. Patients received neither bowel preparation nor anti-spasmodic agents during the MRI examinations. The imaging protocol can be found in Electronic Supplementary Material Appendix A.

The MRI images were retrospectively independently analysed by two experienced abdominal radiologists (F.C.H.B. and C.M. with 12 and 8 years of experience in pelvic imaging, respectively) for parametrial invasion of cervical cancer. They were both blinded to the clinical FIGO stage, the pathology of the included patients, and the results of the other radiologist or previous reports.

The T2W images alone, T2W combined with the DWI images (T2W/DWI), and fusion of the T2W images with high B-value DWI images (fusion T2W/DWI) were evaluated. For half of the patients, T2W was scored first and for the other half T2W/DWI and fusion T2W/DWI was evaluated first. This strategy was used to avoid bias induced by the growing experience of the observer. Second, in order to avoid recall bias, an interval of at least 4 weeks between evaluation of these images was maintained.

The readers were asked to assess the presence of parametrial invasion based on a subjective visual assessment of

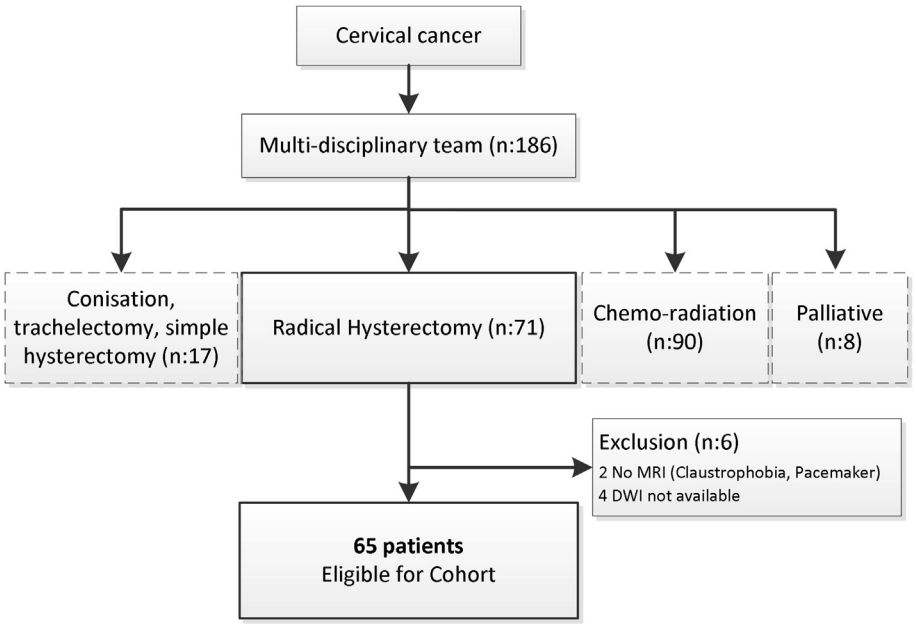

Figure 1 Flowchart patient cohort.

the images using a semi-qualitative six-point confidence scale: 0, definitely no parametrial invasion; 1, probably no parametrial invasion; 2, unclear, but likely no parametrial invasion; 3, unclear, but likely parametrial invasion; 4, probably parametrial invasion; 5 definitely parametrial invasion.

Exclusion of parametrial invasion was considered if the hypointense stromal ring was intact either on T2W or on the fusion images (score 0 or 1).[9] Suspicion of parametrial invasion was raised (score 4 and 5) whenever the stromal ring was disrupted and if tumour signal intensity (nodular or irregular) was seen on the parametrium or bulging in the parametrium.[12] If the stromal ring was disrupted without other signs of parametrial invasion the radiologist scored (2 or 3). These same criteria were used for the diffusion and fusion images. The readers used the criteria as a guideline but were free to interpret the images based on prior experience. An example is shown in Fig 2. For the calculation of performance indices of the diagnostic test, a score of 0–2 was considered a negative result (no parametrial invasion) and a score of 3–5 was considered a positive result (parametrial invasion). Additionally, to subjectively evaluate the increase in certainty between T2W/DWI and fusion T2W/DWI, a five-point Likert scale (observer prevalence rating) was scored. The reference standard was histological results obtained by an experienced gynaecopathologist.

Data management and statistical analysis

Receiver operating characteristics (ROC) curves were constructed to determine the diagnostic performance of T2W MRI, combined T2W/DWI, and fusion T2W/DWI for assessing parametrial invasion in the individual patient. Corresponding areas under the ROC curve (AUCs), sensitivity, specificity, and positive and negative predictive values were calculated according to a predefined cut-off. Sensitivity and specificity for the different scoring methods were compared using the McNemar test for paired data and predictive values were compared by the method of Leisenring *et al.*[18] AUCs were compared according to the method described by De Long *et al.*[19] Interobserver variability was assessed by means of quadratic weighted kappa's: <0.20 poor agreement, 0.20–0.40 fair agreement, 0.40–0.60 moderate agreement, 0.60–0.80 good agreement, and >0.81 excellent agreement.[20]

Prior to evaluation of the prospective cohort study, a sample size calculation was performed. A prevalence of parametrial invasion of 15–25% (based on literature) was taken into account.[6] Second, an AUC of T2W MRI of 0.75–0.80 was expected. Approximately 62 patients were needed to show a difference in AUC of 0.10 (0.8 power and alpha 0.05). To anticipate 10–15% exclusions, a prospective cohort of 71 patients was needed.

Statistical analyses were performed using SPSS Statistics v22.0 (IBM, Armonk, NY, USA), Stata v11.0 (StataCorp LP, TX, USA), and R (version 3.2.3). All *p*-values were two-sided, and a p-value <0.05 was considered statistically significant.

Results

Population

Seventy-one consecutive patients were eligible for this cohort. Two patients were excluded from the cohort as no MRI was performed (claustrophobia or pacemaker) and in four patients no DWI sequences were performed by the referring centre. The baseline characteristics of the remaining 65 patients are listed in Table 1.

After surgery, histological examination identified parametrial invasion in eight patients. In one patient, the

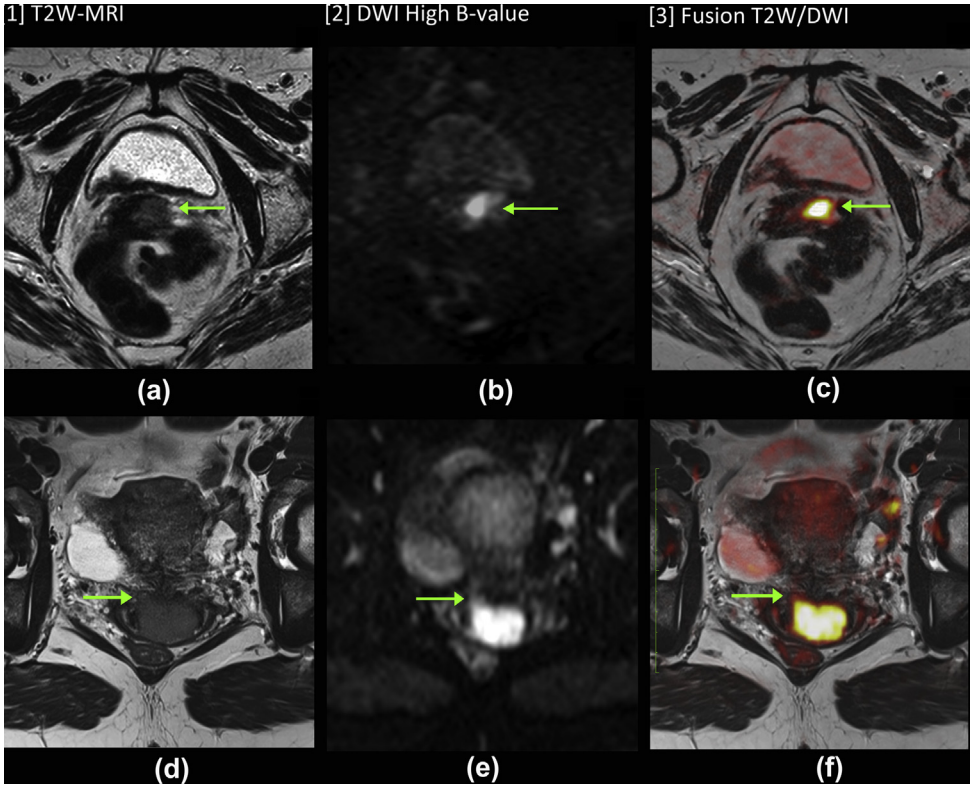

Figure 2 T2W MRI, high b-value diffusion and fusion imaging assessing parametrial invasion for cervical carcinoma. (a,b,c): Left-side pathology-proven parametrial invasion, fusion images (c) increasing certainty. (d,e,f) Both sides at pathology no parametrial invasion. (d) T2W image especially right-side stromal ring not clear, assessed as possible parametrial involvement on the right side. (f) Fusion images downgraded the score to probably no parametrial invasion.

procedure was discontinued because of bulky histologically positive lymph nodes and obvious parametrial invasion, and the patient was therefore included as positive for parametrial invasion. In one patient FIGO stage IIB disease was suspected, chemoradiation would have been first choice of treatment, but this patient did not complete surgery due to excessive tumour blood loss.

Diagnostic performance for assessing parametrial invasion

Table 2 shows the AUC of the ROC curve for assessment of parametrial invasion for T2W MRI, T2W/DWI, and fusion T2W/DWI evaluation. Both observers showed a significant increase in AUC from 0.80–0.67 to 0.94–0.94 when the fusion T2W/DWI was used compared to conventional T2W MRI images (p=0.03 and p<0.01). The AUC for combined T2W/DWI compared to either T2W MRI or fusion T2W/DWI was not significantly different (Table 2). Intra-observer agreement proved to be good in all evaluation methods (kappa 0.58–0.65).

Table 3 shows the diagnostic performance indices for T2W MRI, T2W/DWI, and fusion T2W/DWI evaluation. Sensitivity and specificity increased for both observers when using fusion T2W/DWI. For both observers, the positive predictive value increased significantly compared to T2W image evaluation when fusion T2W/DWI images were available (both p=0.03). No statistically significant differences were found for the other individual parameters. The Likert scale analysis showed that both observers found the additional fusion images useful in 32–34% of patients.

Discussion

This is the first prospective cohort representing daily clinical practice showing that the fusion of T2W MRI with DWI results in an increase in diagnostic performance for the assessment of parametrial invasion in clinical early-stage cervical carcinoma. The increase in performance could possibly be explained by more detailed delineation of the cervical cancer with fusion T2W/DWI, making a better discrimination between tumour, pressure-induced changes, oedema, and/or the biological reaction of the surrounding cervical tissue possible. No significant difference was found between T2W MRI and combined T2W/DWI without fusion; however, a trend in favour of T2W/DWI was shown for all parameters.

Accurate assessment of parametrial invasion to select the patients that should be allocated to chemoradiation therapy is essential.[21,22] If parametrial invasion is recognised after surgery, additional chemoradiation is advised to increase local control and survival,[3] which is associated with more morbidity and higher costs.[4] In the present study, an observed increase in negative and positive predictive values

Table 1
Baseline characteristics (n=65).

Age years (range)	48	(27–82)
FIGO stage (clinical) [a]	IA	3 (4%)
	IB1	53 (82%)
	IB2	6 (9%)
	IIA	2 (3%)
	IIB	1 (2%)
Pathology	SCC	51 (78%)
	ADC	10 (15%)
	ASC	3 (5%)
	CCC	1 (2%)
Time from MRI to operation, weeks (range)	2.7	(0–8)
Parametrial invasion (histology)	8	(12.3%)

All variables are described as mean ± SD or median (IQR) for parameters that were not normally distributed. Proportions (%) were used for categorical values.
SCC, squamous cell carcinoma; ADC, adenocarcinoma ASC, adenosquamous carcinoma; CCC, clear cell carcinoma.
[a] International Federation of Gynecology and Obstetrics (FIGO) 2014 classification.

Table 2
Interobserver agreement (Kappa) and AUC for the assessment of parametrial invasion in cervical cancer.

	Kappa (SD)	AUC (SD)	
		Observer 1	Observer 2
T2W MRI	0.57 (0.12)	0.80 (0.63–0.98)	0.67 (0.48–0.87)
Combined T2W/DWI	0.65 (0.12)	0.85 (0.69–1.0)	0.85 (0.67–1.0)
Fusion T2W/DWI	0.65 (0.12)	0.94 (0.87–1.0)*	0.94 (0.87–1.0)*

* $p<0.05$ compared to T2W MRI.
T2W, T2-weighted; MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging; AUC, area under the receiver operating characteristic curve; SD, standard deviation.

could potentially prevent unnecessary adjuvant treatment after surgery, while increasing the percentage correctly allocated to chemoradiation.

The present results are in line with two previously published studies on this topic.[14,15] Park *et al.* showed in a retrospective study (29% exclusion due to inadequate MRI) in an Asian population a significant increase of the AUC (0.97–0.98) particularly in fusion images compared to T2W images. In accordance with the present study, the positive predictive value for depicting parametrial invasion increased[14]; however, the present study is the first to evaluate this in a prospective cohort.

Interestingly, the difference in the prevalence of parametrial invasion is relatively large; a prevalence of 25% in the study from Park *et al.* in comparison to 12% in the present study. One reason for this difference might be patient selection; 29% of the patient population in the study of Park *et al.*[23] had >IB1 disease compared to only 15% in the present cohort, probably due to a more strict allocation of >IB1 disease to chemoradiation by the multidisciplinary team. As a consequence, the cohort of Park *et al.* could partly be compromised by a relatively large number of patients with an a priori high suspicion of parametrial invasion, facilitating the diagnostic performance of the test. Compared to the present study, they showed a remarkable higher AUC for conventional T2W MRI (0.89–0.91 versus 0.80–0.67 in the present population). A recent meta-analysis supports the assumption: a tendency to increased sensitivity was found within studies that included higher stages cervical cancers.[24] In concordance with the present findings, this systematic review and two recent studies showed a parametrial invasion prevalence of 17% and 12–13%, respectively.[15,16,24] Compared to the present results, the latter two studies showed comparable diagnostic performance (AUC 0.76–0.80) for depicting parametrial invasion solely with conventional T2W MRI.

The only other retrospective study addressing DWI (without fusion) for parametrial invasion found similar results (AUC 0.91–0.95), but their population also consisted of 67% out of patients with FIGO >IB1 carcinomas.[15] In contrast to the present study, fusion between the DWI and T2W images was not performed.

Multiple research groups (ConCerv, GOG-278, and SHAPE) are currently investigating the feasibility of less radical surgery for low-risk cervical cancers.[25–28] DWI could be useful to identify “low-risk” patients as the negative predictive value is high: 96–98% in the present study.[29,30]

The present study has some limitations. First, the study was powered to assess a difference in AUC of 0.10 between conventional and fusion imaging with a prevalence of parametrial invasion of 15–25%. As a consequence, the study was not powered to detect a smaller difference in AUC as seen between combined T2W/DWI and fusion T2W/DWI. In this

Table 3
Diagnostic performance (n=65) for the assessment of parametrial invasion (n=8 on pathological examination) using T2-weighted (W) magnetic resonance imaging (MRI) versus T2W/diffusion-weighted imaging (DWI) and fusion of T2W MRI with DWI.

	Diagnostic performance		PPV	NPV
	Sensitivity	Specificity		
Observer 1 T2W MRI	63 (26–89)	79 (66–88)	29 (11–56)	94 (82–98)
Observer 1 T2W/DWI	88 (47–99)	81 (69–90)	37 (17–61)	98 (88–100)
Observer 1 Fusion T2W/DWI	88 (47–99)	88 (76–95)	50 (24–76)[a]	98 (88–100)
Observer 2 T2W MRI	38 (10–74)	82 (69–91)	23 (6–54)	90 (78–96)
Observer 2 T2W/DWI	63 (26–90)	88 (76–95)	42 (16–74)	94 (83–99)
Observer 2 Fusion T2W/DWI	75 (36–96)	89 (78–96)	50 (22–78)[a]	96 (86–99)

[a] $p<0.05$ compared to T2W MRI.
PPV, positive predictive value; NPV, negative predictive value.

respect, the study was slightly underpowered, but despite the relatively small number of patients with parametrial invasion, a statistical significant increase in AUC was found for fusion T2W/DWI, implying that the positive effect might be even larger than anticipated. Second, as in all cervical cancer studies assessing parametrial invasion, patient selection remains an issue. In retrospect, limiting patient selection to FIGO 1BI tumours (2–4 cm) would have resulted in a more uniform cohort of patients; however, due to the small number of patients, this was not an option as the power would not have been sufficient. Another limitation is that higher stages are allocated to chemoradiation therapy, and therefore, do not undergo surgery, so the sensitivity of the test would be underestimated; however, as the goal was to address the additional value of DWI, this would be the case for both tests. Moreover, a study addressing this issue would be considered non-ethical as this would result in significant triple-modality treatment.

Third, due to the nature of the present study, a prospective cohort representing daily practice with introduction of new MRI systems, DWI was performed on both 1.5 and 3 T machines. Recently, one meta-analysis showed field strength to be an influencing factor in the assessment of parametrial invasion.[24] As diffusion sequences were subjectively assessed and compared with different techniques within the same patient, field strength-induced bias would not be expected to be of major importance in this study. Moreover, multiple studies showed only small differences across field strengths for abdominal imaging even for quantitative analyses.[31] Due to changes in MRI units, five patients were scanned on a 3 T PET-MRI scanner with a different diffusion protocol with the highest B-value of 800. This protocol was implemented to decrease scanning time. Higher B-values are preferred as the ratio of tumour signal–surroundings is less; however, differences were <10% even for quantitative ADC analyses.[32] Therefore, due to the qualitative nature and the relatively small difference in B-value, the present results are not expected to be hampered due to the change in protocol. Changes in imaging protocol are common and reflect general practice. In addition, as patients were imaged on units from different vendors, image quality may vary; however, despite the heterogenic population reflecting general daily practice, fusion T2W/DWI imaging increased the diagnostic performance. Therefore, the present study lowers the threshold for implementation in clinical practice.

Treatment of cervical cancer is evolving to favour less radical surgery, neoadjuvant chemotherapy, and MRI-based brachytherapy. The results of the present study as well as other research groups have shown additional value of MRI in staging of cervical cancer. The present results support the hypothesis that the addition of DWI increases diagnostic performance for the assessment of parametrial invasion even more. When MRI is to be incorporated in a new classification for cervical cancer, DWI should be considered.

In conclusion, the present results show that conventional T2W MRI fused with DWI results in an increase in diagnostic performance for the assessment of parametrial invasion in early-stage cervical carcinoma.

Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crad.2019.07.003.

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