CLÁUDIA CRISTINA CAMISÃO

RESSONÂNCIA MAGNÉTICA NO ESTADIAMENTO E AVALIAÇÃO PROGNÓSTICA DE PACIENTES COM CARCINOMA DE COLO UTERINO TRATADAS COM QUIMIOTERAPIA E RADIOTERAPIA CONCOMITANTES

Dissertação de Mestrado

ORIENTADOR: Prof. Dr. LUIZ CARLOS ZEFERINO

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Dissertação de Mestrado apresentada à Pós-Graduação da Faculdade de Ciências Médicas da Universidade Estadual de Campinas para obtenção do Título de Mestre em Tocoginecologia, área de Ciências Biomédicas

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“ Para ser grande, ser inteiro, nada teu exagera ou exclui.

Ser todo em cada coisa. Põe o quanto és no mínimo que fazes,

“Assim no lago a lua toda brilha, porque alta vive”.

Fernando Pessoa

Sumário

Símbolos, Siglas e Abreviaturas

FIGO	Federação Internacional de Ginecologia e Obstetrícia
IARC	Agência Internacional de Pesquisa do Câncer
INCA	Instituto Nacional do Câncer
MS	Ministério da Saúde do Brasil
OMS	Organização Mundial da Saúde
RECIST	*Response Evaluation Criteria In Solid Tumors*
RM	Ressonância Magnética
TC	Tomografia Computadorizada
USG	Ultra-sonografia
WHO	*World Health Organization*

Resumo

Introdução: A despeito do tratamento para o carcinoma de colo uterino, 30% das mulheres não obtêm resposta total e morrem precocemente, devido à recorrência ou persistência da doença. O método de imagem e o momento ideal para avaliar a resposta terapêutica, bem como fatores prognosticos destas pacientes, permanecem indefinidos. **Objetivo**: Avaliar as contribuições da Ressonância Magnética no estadiamento e na identificação de fatores prognósticos relevantes em pacientes submetidas a tratamento concomitante de quimioterapia e radioterapia, seguido de braquiterapia **Sujeito e métodos**: estudo de coorte longitudinal, com seguimento antes e após o tratamento das mulheres. Foram selecionadas 56 pacientes, com diagnóstico de carcinoma de colo uterino, tratadas com quimioterapia e radioterapia concomitantes seguido de braquiterapia e acompanhadas no HCII – INCA.Todas foram submetidas a Ressonâncias magnéticas seriadas, sendo a primeira no momento do estadiamento, a segunda após o tratamento concomitante e a terceira após a braquiterapia. Os fatores prognósticos estudados foram: volume tumoral e invasão de corpo uterino, medidos na primeira RM. As respostas ao tratamento foram subdividas de acordo com os criterios de RECIST em resposta completa, resposta parcial, doença estável e progressão de doença, e foram mensuradas

no momento da segunda RM após o tratamento combinado e no momneto da terceira RM após a braquiterapia. **Análise estatística**: a concordância foi avaliada através do coeficiente de Kappa. A sobrevida foi avaliada pelo método de Kapplan-Meier e as curvas foram comparadas pelo teste de *log-rank.* Foram utilizados modelos de COX (simples e múltiplos) para calcular o Hazard Ratio. O nível de significância foi de 5% e o *software* utilizado foi o SAS versão 9.1.3. **Resultados**: O índice de Kappa entre estadiamento FIGO e o estadiamento com RM foi de 0,40. Na segunda RM após o tratamento concomitante, 1 paciente apresentou doença estável, 1 progressão de doença, 20 resposta parcial e 21 obtiveram resposta completa. Na terceira RM, após a braquiterapia, 4 tiveram progressão da doença, 4 resposta parcial e 33 obtiveram resposta completa. Pacientes com volume tumoral maior que 50cm^3 tiveram sobrevida global pior. **Conclusão:** A concordância entre o estadiamento FIGO e o estadiamento com RM foi baixa. O volume tumoral mostrou ser um bom preditor de sobrevida global mesmo quando corrigido em análises multivaridas para o estadiamento FIGO. A invasão do corpo uterino mostrou-se limítrofe como fator de sobrevida global.

Summary

Introduction: Despite the available treatment for cervical cancer, 30% of women fail to achieve full response to therapy and die early due to recurrence or persistence of the disease. The ideal imaging method and the optimal time for evaluating therapeutic response, as well as the prognostic factors in these patients, remain undefined. **Objective:** To evaluate the contributions of magnetic resonance imaging (MRI) in staging and in the identification of relevant prognostic factors in patients submitted to treatment consisting of concurrent chemoradiotherapy followed by brachytherapy. The agreement between FIGO and MRI staging was also evaluated. **Subjects and Methods:** A longitudinal, cross sectional study with evaluations prior to and following treatment was carried out in 56 women with a diagnosis of cervical cancer treated with concurrent chemoradiotherapy followed by brachytherapy at the II Cancer Hospital of the National Cancer Institute (INCA). All patients were submitted to serial MRI, the first being carried out at the time of staging, the second following concurrent chemoradiotherapy and the third after brachytherapy. The prognostic factors studied were tumor volume and uterine invasion at first MRI. The responses to treatment were subdivided according to the Response Evaluation Criteria in Solid Tumors (RECIST) into complete response, partial

response, stable disease or disease progression, and were assessed at the time of the second MRI following combined treatment and at the time of the third MRI after brachytherapy. **Statistical Analysis:** Agreement was evaluated using the kappa coefficient. Survival was assessed using the Kaplan-Meier method and the curves were compared using the log-rank test. Univariate and multivariate Cox models were used to calculate the hazard ratios. Statistical significance was defined at 5% and the statistical software package used was SAS, version 9.1.3. **Results:** The kappa index between FIGO staging and MRI-based staging was 0.40. At the second MRI after concurrent chemoradiotherapy, 1 patient was found to have stable disease, 1 had disease progression, 20 had achieved a partial response and 21 had achieved complete response. At the third MRI, following brachytherapy, 4 patients had disease progression, 4 had a partial response and 33 had obtained complete response. Overall survival was poorer in patients in whom tumor volume was > 50 cm^3. **Conclusion:** Agreement between FIGO staging and MRI staging was low. Tumor volume was found to be a good predictor of overall survival even when corrected for FIGO staging in multivariate analyses. Uterine invasion was found to be a borderline predictive factor of overall survival.

1. Introdução

O carcinoma de colo uterino representa a segunda neoplasia maligna mais freqüente em ginecologia; todavia, em alguns países em desenvolvimento as taxas de incidência são tão elevadas que chegam a ocupar o primeiro lugar. São 500 mil novos casos por ano em todo o mundo, sendo que 83% destes casos situados nos países em desenvolvimento (Globocan, 2002). Nos Estados Unidos e na União Européia são diagnosticados cerca de 42.000 casos anualmente deste tipo de câncer. (Arbyn e Ferlay, 2007; Bethesda, 2008). Taxas crescentes têm sido identificadas no Brasil. Em 2008, o Ministério da Saúde do Brasil (MS) estimou 18.680 novos casos no país, somando cerca de 8% de todos os tumores malignos femininos (Brasil, 2008).

O carcinoma de colo uterino também se associa à alta taxa de mortalidade nos países em desenvolvimento, mas pode ser curado quando diagnosticado em estádios iniciais (Ferlay e Pisanni, 2004). Todavia, onde não há bons programas de rastreamento precoce, a maioria das mulheres é diagnosticada em estádios

avançados da doença, como ainda é a situação predominante do Brasil (Thuler e Mendonça, 2005).

O principal desafio enfrentado pelos oncologistas ao diagnosticar um câncer de colo uterino é inicialmente determinar o tratamento mais eficaz e paralelamente formular um prognóstico. Na intenção de gerar uma linguagem universal, a extensão do tumor em geral é expressa através do seu estadiamento. O objetivo principal desta proposta tem sido oferecer uma classificação para a extensão da doença, de modo a permitir que as experiências clínicas, métodos de tratamentos e manejo com a doença possam ser compartilhados internacionalmente sem confusão ou ambigüidade (Benedet *et al*., 2000).

O sistema de estadiamento necessita, portanto, ser embasado no conhecimento mais aprimorado que se tenha disponível em mãos no momento. Isso implica em mudanças que irão ocorrer ao longo do tempo devido à aquisição de novos conhecimentos, pelo desenvolvimento da ciência e de novas tecnologias. A utilização do sistema de estadiamento uniformiza a linguagem, facilitando a investigação clínica e integrando novos dados sobre pacientes semelhantes de diferentes fontes, fornecendo deste modo um idioma comum para compartilhar o conhecimento mundial adquirido (Benedet *et al*., 2000).

Em 1954, a Federação Internacional de Ginecologia e Obstetrícia (FIGO) assumiu e padronizou o sistema de estadiamento dos tumores femininos, que, inicialmente, baseava-se no exame clínico e em exames de imagem de baixo custo, considerando-se principalmente a disponibilidade dos métodos subsidiários

nos diferentes países (Benedet *et al*., 2001). As normas atuais para o estadiamento dos tumores de colo uterino são baseadas no exame clínico; deste modo deve ser realizado um cuidadoso exame clínico em todos os casos, de preferência por um examinador experiente e sob analgesia. O estadiamento clínico não deve ser alterado devido a achados posteriores. Quando houver dúvida em que estádio alocar determinada paciente, os seguintes exames complementares poderão ser utilizados: palpação, inspeção, colposcopia, curetagem endocervical, histeroscopia, cistoscopia, retosigmoidoscopia, urografia, Raios X de tórax e Raios X de esqueleto. Se houver suspeita de invasão de bexiga ou reto, deve ser efetuada uma biópsia para confirmação histopatológica. É importante destacar que a FIGO reconhece que os achados de exames opcionais como: Laparoscopia, Tomografia Computadorizada (TC), Ressonância Magnética (RM) e Tomografia por Emissão de Positons (PET) são importantes para o planejamento terapêutico, mas devido ao fato de serem pouco disponíveis e apresentarem interpretação variável, não devem ser a base para uma mudança no estadiamento (Pecorelli *et al*., 2008).

Todavia, o estadiamento clínico pode não corresponder à real extensão da doença. Entre o estadiamento clínico e o pós-operatório pode haver discrepâncias de até 25% nos estádios iniciais até IB1 e de 65 a 90% nos estádios mais avançados, a partir de IB2 (Subak *et al*., 1995). Estudo mais recente demonstrou uma discordância de 33% entre o estadiamento clínico FIGO e os achados anatomopatológicos (Park *et al*., 2005).

Para superar esta limitação, o Comitê de Oncologia da FIGO passa a recomendar que o estadiamento definitivo seja baseado nos achados do intra-operatório, pelo cirurgião e pelo patologista (Benedet *et al.*, 2001). Todavia, essa regra se aplica adequadamente aos tumores de endométrio e ovário, mas não aos tumores de colo uterino, pois os casos localmente avançados não são submetidos rotineiramente à cirurgia. Deste modo, o estadiamento FIGO para tumores de colo uterino está fundamentado basicamente na extensão anatômica compartimental do tumor, verificada através do exame clínico e exames complementares basicos (Figura 1).

Entretanto existem falhas e limitações. A baixa acurácia e pouca reprodutibilidade do estadiamento são reconhecidas (Ozsarlak *et al.*, 2003). Há dificuldades no exame clínico em mensurar o real tamanho do tumor, especialmente se o tumor primário tiver localização ou componente endocervical. Existe ainda uma imprecisão em determinar a extensão extracervical para o corpo uterino, paramétrio, parede pélvica, órgãos adjacentes e linfonodos que têm mostrado ser de grande importância prognóstica. (Selman *et al.*, 2008).

Para os tumores de colo uterino diagnosticados em estádios avançados e que deste modo não serão submetidos à cirurgia, a avaliação de imagem pré-tratamento qualifica o estadiamento clínico e pode agregar informações para o planejamento terapêutico e avaliação prognóstica (Pannu *et al.*, 2001; Narayan *et al.*, 2003; Takafumi *et al.*, 2008).

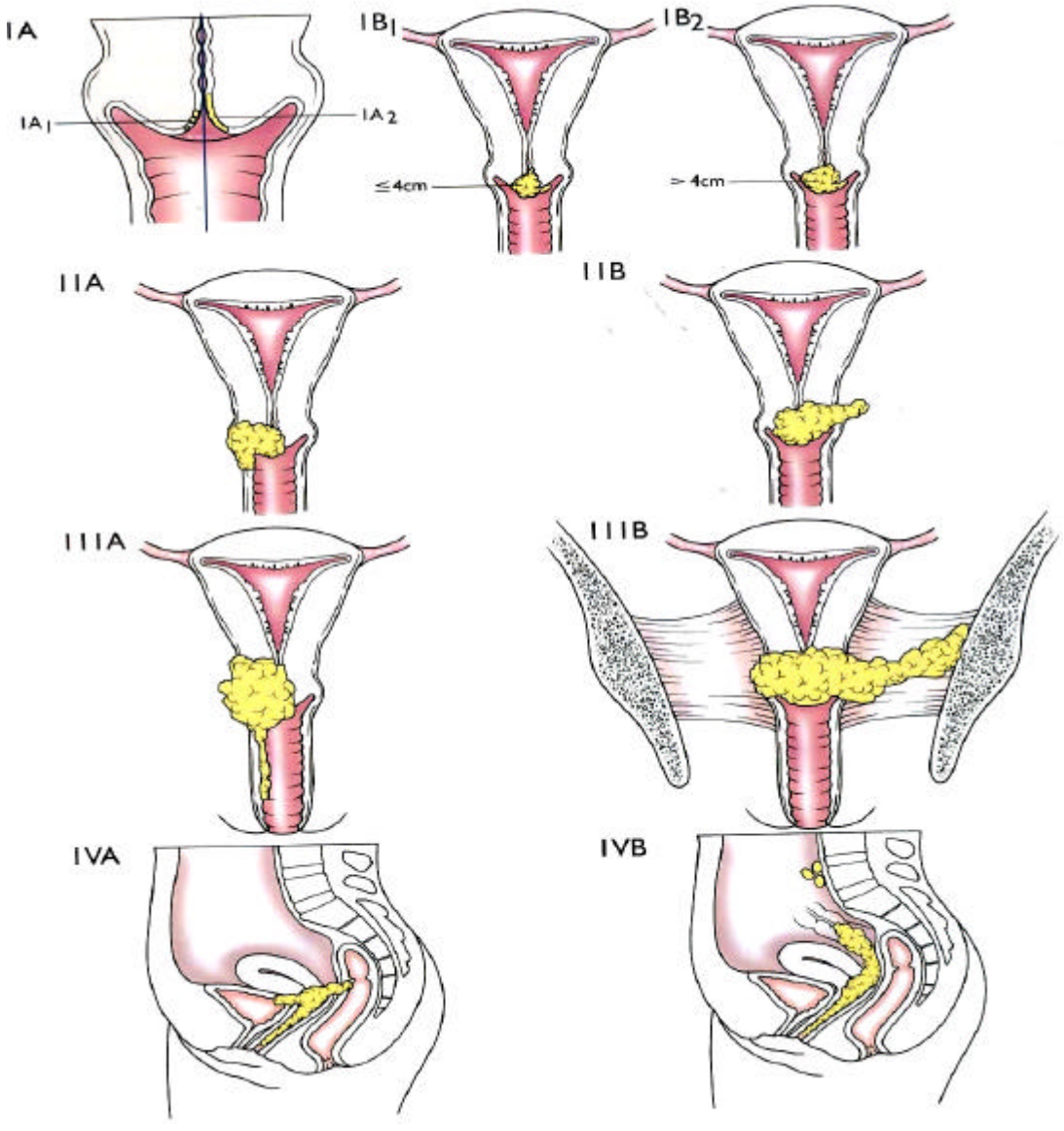

Figura 1: *Estadiamento segundo a FIGO.*

O tratamento cirúrgico padrão do estadiamento I B1/ II A (<4 cm) é histerectomia abdominal radical e linfadenectomia. Alternativamente, o tratamento-padrão é radioterapia externa acrescida de braquiterapia. Para tumores mais

avançados, o tratamento concomitante de quimioterapia baseada em platina e radioterapia externa, e posteriormente braquiterapia, tem sido mais comumente utilizado (Rose *et al.*, 1999; Green *et al.*, 2001; Eifel *et al.*, 2004).

O Comitê de Oncologia da FIGO recomenda várias possibilidades de associações terapêuticas, entretanto, a maioria dos serviços de tratamento oncológico tem utilizado para os casos de carcinoma de colo uterino localmente avançado, a radioterapia externa concomitante à quimioterapia, seguida de braquiterapia (Benedet *et al.*, 2000; Peters III *et al.*, 2000).

A despeito dos avanços na abordagem radioterápica e quimioterápica, que resultou em menor morbidade e melhores taxas de sobrevida, cerca de 30% das pacientes com carcinoma de colo, submetidas ao tratamento, ainda morrem como resultado de recorrência ou doença persistente (Benedet *et al.*, 2001; Quinn *et al.*, 2006; Delpech *et al.*, 2007). Isso, pelo menos em parte, pode ser devido à subestimação da doença e ao não reconhecimento precoce da recidiva tumoral. A escolha do tratamento depende fundamentalmente da extensão da doença no momento do diagnóstico e, deste modo, um estadiamento acurado e preciso mostra-se essencial para a escolha do tratamento adequado (Holtz *et al.*, 2002; Yen *et al.*, 2008).

No intuito de se aprimorar a programação terapêutica através de um estadiamento mais preciso, ferramentas diagnósticas de imagem têm sido propostas, como a Tomografia Computadorizada e a Ressonância Magnética (Narayan, 2005; Koyama *et al.*, 2007). Questiona-se o quanto relevante é um

sistema de estadiamento baseado em achados clínicos, em uma era em que uma grande variedade de sofisticados exames de imagem estão disponíveis. Porém, não existe ainda uma sistematização para a utilização destes métodos de imagem e a decisão fica na dependência, principalmente, da disponibilidade dos exames no serviço de Oncologia (Amendola *et al.*, 2005; Allen e Narayan, 2005). O planejamento terapêutico, embasado na TC e na RM, tem sido instituído em vários centros radioterápicos, sendo que o grupo de trabalho GEC-ESTRO publicou recomendações de utilização da RM no planejamento da braquiterapia (Potter *et al.*, 2006). Existem diversos estudos mostrando a superioridade da TC e da RM frente ao estadiamento clínico FIGO. Apesar disso, até o momento, nenhum destes métodos de imagem mais sofisticados foi incorporado pela FIGO como sugestão para o auxílio do estadiamento ou do planejamento radioterápico (Bipat *et al.*, 2003; Okamoto, 2003; Mitchell, 2006; Sahdev, 2007).

A TC é um método mais amplamente difundido e disponível, possui custo inferior à RM e à Tomografia por emissão de positons, sendo mais facilmente realizado pelas pacientes, pois requer tempo de aquisição menor e menos suscetível a artefatos. Apresenta boa sensibilidade e especificidade para detecção de linfonodos retroperitoneais, sendo exame de rotina no estadiamento de tumores em muitas instituições que realizam tratamento oncologico (Kim *et al.*, 1994).

Todavia a RM, por ter melhor resolução espacial e maior diferenciação tecidual, fornece mais detalhes no exame da pelve do que a TC e, portanto, oferece maior definição no dimensionamento da lesão primária, extensão da doença, linfonodos na pelve, envolvimento vaginal e da musculatura pélvica

(Lam *et al.*, 2000; Follen *et al.*, 2003). O uso da RM antes do tratamento tem se mostrado de grande valor para um estadiamento mais preciso, confiável, e promissor na predição dos resultados terapêuticos (Tanaka *et al.*, 2000).

Desde a introdução da RM no auxílio ao estadiamento dos tumores de colo uterino por Hricak (Hricak *et al.*,1988) e Togashi (Togashi *et al.*,1989), no final dos anos 80 até o momento, muito se evoluiu no desenvolvimento tecnológico de equipamentos, bobinas dedicadas à pelve, agentes de contraste e seqüências, melhorando a qualidade da imagem produzida. Togashi e colaboradores estabeleceram uma correlação entre o estadiamento clínico FIGO e os achados de imagem nos exames de RM realizados antes do tratamento (Quadro 1). As contribuições da RM no estadiamento, bem como no planejamento radioterápico, estão hoje mais bem definidas (Barillot *et al.*, 2006; Dimopoulos *et al.*, 2006).

Nos países em desenvolvimento o número de pacientes com chance de ter invasão de bexiga e reto é maior, pois em geral a doença é encontrada em estádios mais avançados. Estudos têm demonstrado valor preditivo negativo de 96% a 100% para invasão de bexiga e reto com o uso da RM (Hricak *et al.*, 1988; Liang *et al.*, 2000; Chung *et al.*, 2001). Mais recentemente, Rockall et al. encontraram sensibilidade de 100% para invasão de reto e bexiga e especificidade de 91% e 88%, respectivamente, associado a 100% de valor preditivo negativo para ambos. Assim, esses indicadores de desempenho permitem dispensar a realização de enema, urografia, cistoscopia e retosigmoidoscopia nas pacientes com RM negativa para invasão de reto e bexiga, promovendo uma redução da morbidade e do custo no manejo da doença (Rockall *et al.*, 2006).

Quadro 1: Correlação do estadiamento FIGO do câncer de colo uterino com achados de RM

Estádio		RM seqüência T2
Ia	Microinvasor	Não há evidência de tumoração
Ib	Invasivo, confinado ao colo	Tumor hiperintenso em T2, contrastando com o sinal hipointenso do estroma cervical
Ib1	Lesão clinicamente visível de até 4cm	Tumor substitui parcial ou totalmente o estroma cervical, que é hipointenso, e não ultrapassa a interface parametrial representada por halo hipointenso
Ib2	Lesão clinicamente visível maior que 4cm	
IIa	Tumor invade terço superior da vagina, mas não compromete o terço inferior	Interrupção segmentar do hipossinal do terço superior da parede vaginal
IIb	Tumor invade o paramétrio, mas não a parede pélvica nem o terço inferior da vagina	Tumor hiperintenso interrompendo o halo hipointenso da interface do estroma cervical com o paramétrio
IIIa	Envolvimento do terço inferior da vagina, sem comprometimento da parede pélvica	Interrupção segmentar do hipossinal do terço inferior da parede vaginal
IIIb	Envolvimento da parede pélvica ou hidronefrose	Tumor estendendo a musculatura (obturador interno, piriforme ou elevador do ânus) ou promovendo hidroureter
IVa	Tumor invade a mucosa da bexiga ou do reto	Perda do sinal hipointenso da parede interna (mucosa) da bexiga ou do reto
IVb	Metástase a distância	Metástase a distância

Apesar do amplo uso na prática ginecológica, uniformizando e facilitando a comunicação entre médicos, o estadiamento FIGO não se mostra eficaz o suficiente para avaliar o prognóstico e o resultado terapêutico, ou mesmo a sobrevida das pacientes com tumor de colo uterino. Há algumas evidências de que o estadiamento com o auxílio da RM pode estabelecer melhor prognóstico

do que somente o estadiamento clínico em pacientes com tumores de colo uterino avançado (Taylor *et al.*, 2003).

Além da otimização do estadiamento pré-operatório existe a necessidade objetiva de se ter uma ferramenta efetiva para avaliar o efeito da radioterapia e quimioterapia, bem como detectar, o mais precocemente possível, tumores residuais e recorrência durante o tratamento e acompanhamento dessas mulheres (Kodaira *et al.*, 2003; Babar *et al.*, 2007). Esta avaliação de resposta terapêutica deveria ser feita ainda durante o tratamento, a tempo de se poder intervir e fazer um resgate destas pacientes, visando melhorar o prognóstico (Boss *et al.*, 2001).

Todavia, esta avaliação tem sido realizada clinicamente, o que retarda a detecção de tumores residuais e recidiva. Mais ainda, é preciso estar atento à possibilidade de alternativas de avaliação prognósticas, pois os parâmetros histopatológicos que serviam anteriormente não podem ser utilizados nas pacientes com tumores de colo uterino avançados, pois estas em geral não são submetidas à cirurgia (Landoni *et al.*, 1997; Rose *et al*, 1999; Pearcey *et al.*, 2002).

O tamanho tumoral, o *status* linfonodal na pelve, bem como a invasão para corpo uterino pelo tumor primário em achados cirúrgicos são fatores prognósticos significativos e determinantes na sobrevida e na predição de falha terapêutica (Delgado *et al.*, 1990; Burghardt*et al.*, 1992; Zaino *et al.*, 1992). Apesar de estes fatores não serem levados em conta no sistema de estadiamento FIGO, muitos estudos estimam que possuem maior relevância prognóstica que os achados clínicos (Yamashita *et al.*, 2000; Kupets, 2001).

A mensuração do volume tumoral através da RM, antes de se iniciar o tratamento, tem sido alvo de estudos para definir a população de mulheres de alto risco para doença residual ou recorrência. Evidências indicam ser este um fator potente na predição dos resultados terapêuticos e sobrevida destas pacientes (Takafumi *et al.*, 2008). Estudo com pacientes tratadas com radioterapia exclusiva e submetidas à RM seriadas (antes, durante e após a radioterapia) demonstrou que a taxa de regressão comparativa do volume tumoral nestes três momentos pode ser utilizada como fator preditor dos resultados e da sobrevida destas pacientes (Mayr *et al.*, 2002). Nan e colaboradores ratificaram esses achados e afirmam que a taxa de regressão do volume tumoral no meio do tratamento de pacientes submetidas à quimioterapia e radioterapia combinadas é um fator preditor do controle de doença local (Nam *et al.*, 2007).

Deste modo, o grande desafio é tentar reproduzir os parâmetros prognósticos que conseguimos retirar dos achados cirúrgicos, nas pacientes não submetidas à cirurgia através dos exames de RM. Soutter e colaboradores analisaram o volume tumoral em 126 pacientes portadoras de tumor de colo uterino avançado através de RM antes do tratamento e concluíram que o volume tumoral, isoladamente, é o mais forte fator preditor de sobrevida, superior aos achados clínicos e histopatológicos previamente usados. Sugeriu ainda ser a sobrecarga do tamanho tumoral mais determinante para o resultado terapêutico do que a própria invasão através das margens anatômicas uterinas (Soutter *et al.*, 2004).

Assim como o volume tumoral, a invasao do corpo uterino pelo tumor de colo uterino também tem sido alvo de estudos como fator associado à resposta

terapêutica e sobrevida. Amano e colaboradores afirmaram que o envolvimento do corpo uterino na RM antes da quimioterapia neo-adjuvante indicaria uma pior resposta ao tratamento. Narayan e colaboradores em 2006 chegam à mesma conclusão em um grupo de pacientes tratadas cirugicamente ou com radioterapia (Amano *et al.*,1998; Narayan *et al.*, 2006). Mais recentemente, e já com o advento da quimioterapia concomitante a radioterapia, Kim e colaboradores afirmam que tanto o volume tumoral quanto a invasão do corpo uterino pelo tumor são fatores prognósticos importantes e que a invasao do corpo uterino aumentaria as chances de metástases paraórtica e supraclavicular, bem como reduziria a sobrevida global e livre de doença (Kim *et al.*,2007).

Para se avaliar melhor a resposta ao tratamento em tumores sólidos dispõe-se de alguns critérios denominados “Response Evaluation Criteria In Solid Tumors” (RECIST), que são amplamente usados nos estudos seriados de TC e RM para portadores de tumores sólidos que necessitam de avaliação de resposta ao tratamento quimioterápico. Tais critérios classificam a resposta ao tratamento em quatro categorias: completa, parcial, progressão de doença ou doença estável nos exames de segmento durante e após a terapêutica. (Therasse *et al.*, 2000). O Anexo 1 mostra os critérios de RECIST.

Se com a contribuição da RM no momento do estadiamento ou mesmo durante o tratamento através dos fatores prognósticos relevantes como volume tumoral, invasão corporal, presença de linfonodos suspeitos ou taxa de regressão tumoral, pudermos selecionar a população de mulheres que potencialmente não responderão ao tratamento inicialmente proposto, teremos a possibilidade de mudar

a abordagem terapêutica, melhorar o prognóstico e reduzir as morbidades destas pacientes.

Portanto, a proposta do presente estudo é avaliar as contribuições da ressonância magnética no estadiamento e avaliação prognóstica de mulheres com câncer do colo do útero tratadas com quimioterapia e radioterapia concomitantes, através de exames de RM seriados, antes, durante e após o tratamento, utilizando-se a padronização estabelecida pelos critérios de RECIST.

2. Objetivos

2.1. Objetivo geral

Avaliar as contribuições da Ressonância Magnética no estadiamento e na avaliação prognóstica em pacientes portadoras de carcinoma de colo uterino submetidas à quimioterapia e radioterapia concomitantes.

2.2. Objetivos específicos

1- Avaliar a concordância entre o estadiamento clínico FIGO e o estadiamento obtido na RM pré-tratamento.

2- Identificar parâmetros prognósticos na RM realizada no estadiamento que possam predizer a falha terapêutica.

3- Avaliar se a resposta terapêutica mensurada após tratamento combinado de quimioterapia e radioterapia externa, expressa sob a forma dos critérios de RECIST, possui relevância prognóstica.

4- Avaliar se a resposta terapêutica mensurada após a braquiterapia, e expressa sob a forma dos critérios de RECIST, possui relevância prognóstica.

3. Publicação

Prognostic factors assessed by magnetic resonance imaging for cervical carcinoma treated with concurrent chemoradiotherapy

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Original Article:

Prognostic factors assessed by magnetic resonance imaging for cervical carcinoma treated with concurrent chemoradiotherapy

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Abstract

Objective: The aim of this study was to identify relevant prognostic factors in magnetic resonance imaging (MRI) for the staging of cervical cancer, following concurrent chemoradiotherapy and after brachytherapy. The agreement between FIGO and MRI staging was also evaluated. **Methods:** Fifty-six patients with FIGO stage IB2 to IIIB were selected and submitted to serial MRI at staging (MRI-1), after concurrent chemoradiotherapy (MRI-2) and 8 weeks after brachytherapy (MRI-3). Response to chemoradiotherapy was quantified using the Response Evaluation Criteria in Solid Tumors (RECIST). **Results:** The kappa coefficient between FIGO and MRI staging was 0.40. At MR-1, the patients with tumor volume = 50 cm^3 had poorer overall survival (Hazard ratio: 4.92; 1.09–22.12). At MRI-2, following concurrent chemoradiotherapy, 1 patient had stable disease, 1 had disease progression, 20 had a partial response and 21 had a complete response to treatment. At MRI-3, following brachytherapy, 4 patients had disease progression, 4 had a partial response and 33 a complete response to treatment. Overall survival was poorer in patients in whom tumor volume was $\geq 50cm^3$. **Conclusions:** Agreement between FIGO and MRI staging was fair. Tumor volume was good predictor of overall survival. Uterine body invasion as a predictive factor of overall survival had only borderline statistical significance. Response to treatment at MRI 2 and MRI 3 showed no prognostic value with respect to overall survival, nevertheless it was possible to identify those patients who had not responded adequately to treatment at an early stage.

Keywords: Cervical cancer; MRI; prognostic factors; chemoradiotherapy.

Introduction

Despite screening programs, cervical cancer remains one of the major public health issues worldwide with half a million new cases annually[1]. According to the International Federation of Gynecology and Obstetrics (FIGO), staging of cervical carcinomas should be based on clinical findings and simple imaging tests such as x-rays, urography, opaque enema and cystoscopy. Despite widespread use in gynecological practice, FIGO staging has not been shown to be sufficiently effective in evaluating the prognosis and therapeutic outcome of patients with cervical tumors [2].

With the intention of improving therapeutic planning, diagnostic imaging tools such as computed tomography (CT) and magnetic resonance imaging (MRI) have been proposed, the latter appearing to offer certain advantages over the former [3-5]. Staging with the help of MRI permits better evaluation of the extent of the disease compared to clinical staging in patients with cervical carcinoma[3]. Moreover, evidence suggests that tumor volume and uterine body invasion may be powerful predictive factors of therapeutic outcome and survival in these patients [6-10].

With the advent of concurrent chemoradiotherapy in the treatment of cervical cancer, an improvement occurred in morbidity and an increase in the survival rates of patients with advanced disease [10,11]. Nevertheless, these patients are unable to benefit from the histopathological parameters obtained in operable carcinomas since they are not submitted to surgery [12,13]. Therefore, it is important to qualify staging in order to define the extent of the disease and identify more effective prognostic factors. It would then be feasible to identify women who would respond poorly to the proposed treatment, thereby enabling changes to be made in therapeutic management or new therapies to be tested in an attempt to improve the outcome [14,15].

The objective of this study was, therefore, to identify prognostic factors obtained using MRI exams carried out at initial staging, after concurrent chemoradiotherapy and following treatment completion with brachytherapy in patients with advanced cervical carcinoma. It would be of high clinical relevance to identify prognostic parameters that would be applicable to this therapeutic management using MRI, particularly to compensate for the absence of surgical specimens and anatomopathological data in such cases.

Subjects and Methods

Study design and patient population

A prospective, longitudinal cohort study was carried out at the National Cancer Institute (INCA), Rio de Janeiro, Brazil between December 2004 and October 2005 in 56 consecutively admitted patients with cervical carcinoma and clinical staging FIGO IB2 to IIIB. According to the current protocol of the INCA, these patients are submitted to concurrent chemoradiotherapy followed by brachytherapy. Biopsies of all the patients were reviewed by the Pathology Department. The patients were submitted to three MRI exams, the first carried out during initial staging, the second immediately following concurrent chemotherapy and radiotherapy, and the third MRI eight weeks after brachytherapy. This study was approved by the Internal Review Board of INCA and all patients signed the Informed Consent Form prior to inclusion in the study.

Staging

All the patients were clinically staged by gynecological oncologists in accordance with FIGO recommendations that included clinical pelvic examination carried out under analgesia, chest x-ray, cystoscopy and rectosigmoidoscopy. Biopsies were performed

whenever suspicious lesions were found. For the purposes of this study, MRI staging was based on the correlation described by Togashi[16]. The patients in whom there was a loss of signal in the internal wall of the bladder or rectum were considered stage IVA according to MRI. Patients in whom the cervical lesion extended beyond the isthmus in at least two planes in the T2-weighted turbo spin-echo (TSE) sequences were considered to have uterine body invasion (Figure 1).

Concurrent chemotherapy and radiotherapy

All the patients were submitted to weekly chemotherapy with Cisplatin (at a dose of 40 mg/m^2; maximum 70 mg) administered intravenously for five consecutive weeks, and concurrent external radiotherapy administered using an isocentric linear accelerator. The total prescribed dose of external radiotherapy was 45 Gy in 20 fractions over four weeks. The patients were treated in the prone position, the upper border of the radiation field being the L2-S1 junction and the lower border the obturator foramen. Intracavitary radiotherapy was applied using brachytherapy insertions with iridium-192 (192Ir) immediately following concurrent therapy. The total dose was 30.6 Gy delivered to point A.

MRI protocol and analyses of exams

MRI examinations were performed using a 1.5 Tesla superconducting magnet (Symphony, Siemens Medical Systems, Erlangen, Germany). All the exams were reviewed by at least two radiologists who issued a report in consensus. All the patients received 20 ml of intravaginal gel applied by syringe. The protocol used included:

- Spin-echo T1-weighted axial sequence covering abdomen and pelvis; repetition time/ echo time (TR/TE)5.2/2.6ms; slice thickness 3-5 mm; interslice gap 0; matrix 512X512; field of view 380mm using body coil.
- Fast spin-echo T2-weighted were obtained through the pelvis using a phased array coil in sagittal, coronal and axial planes; TR/TE 4500-5000/95-116 ms; slice thickness 3mm; interslice gap 0,2 mm; matrix 512X512; field of view 250 mm.
- The protocol also includes a Turbo Spin echo T2 with fat suppression axial; TR/TE 4500-5000/ 95-116 mm; slice 5 mm; interslice 0,2mm; matrix 512X512; field of view 300-450mm.
- T1-weighted spin-echo axial sequences were acquired before and following intravenous injection of gadolinium (0.1 mmol/kg) TR/TE 5.2/2.6 ms; slice thickness 3 mm; interslice gap 0; matrix 512 x 512; field of view 350 mm.

The first MRI exam (MRI-1) was carried out in all 56 patients within two weeks after clinical staging according to FIGO criteria. The second MRI (MRI-2) was performed in 43 patients immediately following concurrent chemoradiotherapy and always prior to commencing brachytherapy. The third MRI (MRI-3) was carried out in 41 patients between 8 and 10 weeks after brachytherapy. The primary tumors were identified at MRI in all 56 patients.

Tumor volume was measured in cm^3 using the formula: Volume = CC x A-P x R-L x 4/3; product of the craniocaudal (CC) diameter of the tumor obtained parallel to the long axis of the uterus, right-left (R-L) diameter, and anteroposterior (AP) diameter by consensus of at least two experienced radiologists (Figure 2).

Patient follow-up

The duration of patient follow-up varied from 4.3 to 38.8 months with a mean of 20.2 months. Consultations at the gynecological oncology clinic following the end of brachytherapy were carried out at 6-week intervals for the first 6 months, at 3-month intervals until the end of the second year and at 6-month intervals thereafter. Follow-up visits included clinical and gynecological examinations with biopsies whenever suspicious lesions were found. CT or MRI, cystoscopy, rectosigmoidoscopy and biopsies of suspicious lesions were carried out whenever deemed necessary by the gynecological oncologist. All patients with suspicious residual lesions or in whom new lesions were detected at one of the MRI scans performed during the study were submitted to directed biopsy for histopathological confirmation. Based on the MRI-2 and MRI-3 findings, response to treatment was classified in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) categories as: complete response, partial response, stable disease or disease progression [17] (Figure 3).

Statistical analyses

Agreement between clinical staging and MRI staging was evaluated using the kappa coefficient. Kappa coefficients were calculated with their respective 95% confidence intervals and, in accordance with the definitions of Landis and Koch, were classified as poor agreement when < 0, slight when between 0.00 and 0.20, fair when between 0.21 and 0.40, moderate when between 0.41 and 0.60, good when between 0.61 and 0.80 and almost perfect agreement when between 0.81 and 1.00[18].

Survival curves were built using the Kaplan-Meier method and the differences tested using the log-rank technique [19]. Analysis of prognosis was carried out by calculating

the hazard ratio (HR) for the risk of death. Univariate and multivariate Cox proportional hazard models were used to calculate the crude and adjusted hazard ratios throughout the study period. Significance level was defined at 5%. The software package used was the Statistical Analysis System, version 9.1.3 (SAS Institute, Inc., Cary, NC, USA).

Results

The characteristics of the patients, the tumors and the distribution of FIGO staging are shown in Table 1. The age median of patients was 51 years (range 23-75 years). The most frequent histological type of tumor was squamous cell carcinoma, which was diagnosed in 46 patients (82%), followed by adenocarcinoma in 7 patients (13%). The distribution of women according to FIGO staging was 12%, 46% and 41% for stages I, II and III, respectively. Tumor volume prior to treatment ranged from 0.8 cm^3 to 265.2 cm^3, with a median of 63.4 cm^3. In the majority of patients (61%), tumor volume was = 50 cm^3 and in 55% uterine body invasion was present (Table 1).

Analysis of the agreement between FIGO staging and staging based on MRI findings showed a Kappa coefficient of 0.40 (95%CI: 0.26 – 0.53), which is borderline between fair and moderate agreement. FIGO staging and the staging according to MRI-1 findings were concordant in 33 out of 56 patients (59%). MRI-1 findings resulted in more advanced stages for 6/7 FIGO stage I patients (86%), 7/26 (27%) stage II and 6/23 (26%) stage III patients (Table 2).

Thirteen patients were excluded from the analysis of prognosis, one because she was pregnant, one because she was positive for the human immunodeficiency virus (HIV), four because they did not undergo MRI-2 or MRI-3, and seven because they did not undergo the proposed treatment. The patients with tumor volume = 50 cm^3 had poorer

overall survival compared to the group in which tumor volume was < 50 cm^3. The HR was 4.92 (1.09 – 22.12) (Table 3) and the log-rank test showed a p-value < 0.0001 (Figure 4). Patients with uterine body invasion identified at MRI-1 had lower overall survival compared to the group without uterine body invasion; however, statistical significance was borderline. The HR was 3.06 (0.94 – 9.89) (Table 3) and the Kaplan-Meier log-rank test for survival showed a p-value of 0.05 (Figure 5).

MRI-2, carried out at the conclusion of concurrent treatment and prior to brachytherapy, showed complete response (CR) in 20 patients, partial response (PR) in 21, stable disease (SD) in 1 patient and disease progression (DP) in one (Table 1). MRI-2 findings showed no prognostic value either according to the HR (Table 3) or the log-rank test (Figure 6).

MRI-3, carried out 8-10 weeks after the end of brachytherapy, showed CR in 33 patients, PR in 4 and DP in another 4 (Table 1). Taking complete response as reference, the finding of partial response had a non-significant HR of 2.92 (0.59 - 14.61), while the finding of disease progression had a very high HR albeit with a wide confidence interval: 81.18 (8.49 – 775.77). The log-rank test, including the three survival curves for RECIST report from MRI-3, failed to show any statistically significant prognostic association (Table 3, Figure 7).

Patients with FIGO staging I or II with tumor volume = 50 cm^3 had a poorer prognosis compared to patients in whom tumor volume was < 50 cm^3, with a HR of 8.83 (1.05 – 74.15). Patients with tumor volume < 50cm^3 with staging III compared to patients with staging I or II showed HR of 9.90 (1.05 – 74.15); the inconclusive results and very large confidence interval was due to very few cases in this category. The other analyses carried out between FIGO staging and tumor volume showed no statistically significant association (Table 3). Analysis of tumor volume adjusted for FIGO staging and analysis

of FIGO staging adjusted for tumor volume showed no prognostic association according to the Cox proportional hazard ratio (Table 3). The log-rank test including the patients with FIGO staging I or II grouped according to tumor volume failed to show any statistically significant association (Figure 8).

Discussion

According to the results of this study, tumor volume as assessed by baseline MRI is an important prognostic factor for patients with advanced cervical cancer who have undergone concurrent chemoradiotherapy plus brachytherapy. Overall survival was poorer in patients in whom tumor volume was = 50cm^3 (HR = 4.92; 1.09 - 22.12). Stratifying according to FIGO staging, patients with stage I or II tumors and tumors = 50cm^3 in diameter had a poorer prognosis (HR=8.83; 1.05 - 74.15); however, in the case of stage III tumors, volume was not a prognostic factor.

Similar results have been reported for pretreatment MRI scans; however, in most of these studies, there were differences in the study sample and in treatment management. Amano et al. evaluated the accuracy of MRI in predicting the response of invasive cervical carcinoma to systemic neoadjuvant chemotherapy in 41 patients, and reported that complete replacement of cervical stroma by the carcinoma and uterine body invasion by the tumor, as observed at pretreatment MRI, were found to be statistically significant factors in the prediction of tumor response. No difference in tumor reduction was found between the second course and the third or fourth course of chemotherapy. Ten patients were submitted to surgery and estimates of tumor volume made by MRI following chemotherapy were within 5 mm of the resected samples[(20)]. Wagenaar et al. analyzed 126 patients treated by radical surgery, radiotherapy or a combined approach

based on clinical FIGO stage and individual patient criteria, and reported that tumor diameter and volume, as determined by pretreatment MRI scans, were predictive of progression-free survival for patients with invasive cervical carcinoma [21].

Soutter et al. evaluated pretreatment tumour volume as a predictor of survival in patients with cervical cancer in order to delineate small-volume disease in 106 women with invasive carcinoma of whom 88 were submitted to surgery for stage I carcinoma. These investigators reported that stage, type of treatment, lymphovascular space involvement, invasion of the parametrium, closeness of the excision margin, lymph node metastases and MRI measurements of tumour volume, parametrial invasion and lymph node disease were all significantly associated with survival in the univariate analysis, but only MRI measurement of tumour volume remained consistently and strongly associated with survival after multivariate analysis of parameters available prior to treatment. They also suggested that a cutoff volume of around 13cm^3 would be predictive of survival with a positive predictive value of 0.93 and a negative predictive value of 0.75[22]. The present study included women with non-operable cervical cancer with a median tumor volume of 63.4 cm^3, while the median tumor volume in the study reported by Soutter et al. was 4.75cm^3. Therefore, we did not have pathological information to estimate the predictive values and to establish a more accurate cutoff limit for tumor volume as a predictive factor of survival. A tumor volume of 50 cm^3, which was below the median volume of patients in this study, was established as the cutoff limit for analyses to separate the smaller tumors (39% of cases) from the very large tumors.

Narayan et al. studied patients with advanced cervical cancer who underwent pretreatment MRI evaluation, and found that FIGO stage, clinical estimation of tumor diameter, uterine body invasion and tumor volume were significantly correlated with overall survival in

the univariate analyses. However, only uterine body invasion and tumor volume were significantly and independently associated with overall survival in the multivariate analyses [7]. In agreement Kim et al. showed that in patients undergoing concurrent chemotherapy and radiotherapy, a larger tumor volume and uterine body invasion determined by using MRI before starting treatment had a statistically significant relationship to a worse overall survival and disease free survival Also, patients with endometrial invasion had a significantly increased risk of paraaortic and supraclavicular metatastasis. Additionally, they indicated that FIGO stage, clinical tumor diameter and tumor histology had a poor relationship with prognosis by multivariate analysis [8]. In our present study, uterine body invasion showed an HR of 3.06 (0.94 - 9.89) and log-rank test of 0.05, which was considered to be of borderline significance.

Currently, concurrent chemoradiotherapy is widely used for the treatment of patients with stage IB2 or higher cervical cancer [10,11,23,24]. For these patients who are unable to benefit from the prognostic value of histopathological findings, prognostic data are usually obtained too late, generally months after treatment when the opportunity to modify curative treatment has already been missed.

Studies involving serial MRI scans during and after treatment have also shown that tumor volume is the best parameter for the evaluation of prognosis in cervical cancer [6]. Nam et al. evaluated 43 patients treated with radiotherapy (RT) alone and 38 patients treated with concurrent chemoradiotherapy who underwent three serial MRI scans: at the start of RT, at 36-45 Gy of external RT and 1 month after the end of RT. These investigators reported that tumor volume regression rate at 36-45 Gy of external RT was a predictor of the local control rate in both radiotherapy and concurrent chemoradiotherapy. In the patients who were treated with concurrent chemoradiotherapy, the local control rate

difference was greater according to post-RT residual volume than according to the mid-RT tumor regression rate[25].

In the present study, RECIST (Response Evaluation Criteria in Solid Tumors) was applied to assess disease status at termination of concurrent chemoradiotherapy and before brachytherapy. Complete response was found in almost half the patients and partial response was also achieved in a similar proportion; however, this information did not contribute towards predicting overall survival. The MRI findings detected one patient with persistence of disease and one with disease progression, enabling treatment to be revised earlier in these cases. With respect to the MRI-3, the RECIST report of complete response and partial response also failed to contribute towards predicting overall survival; however, the finding of disease progression showed an HR of 81.18 (8.49 - 775.77). Longer follow-up is required to conclusively define whether partial response is predictive of prognosis.

The mean duration of follow-up until the end of this analysis was 20.2 months (range 4.3 - 38.8 months). The short duration of follow-up of the patients limited the statistical power of the analyses, and therefore only the most significant associations were demonstrable. Longer follow-up shall reveal other less significant predictive factors of prognosis with respect to these women and this treatment.

Since MRI has excellent spatial resolution, it is more adequate for the evaluation of the extent of the disease than the FIGO staging parameters [3, 10, 26-28]. It is important to re-emphasize that FIGO recognizes that the findings of optional exams such as laparoscopy, CT, MRI and positron emission tomography (PET) are important in therapeutic planning; however, due to the fact that they are not widely available and that the interpretation of the results is variable, they should not, therefore, be used as a basis for a change in

staging [29]. Hence, clinical staging may not correspond to the true extent of the disease. A recent study showed a disagreement of 33% between clinical staging according to FIGO criteria and anatomopathological findings [30]. Another study that compared clinical staging with staging evaluated by MRI found that staging was concordant in only 25% of cases [3].

In the present study, FIGO staging and staging based on MRI findings were concordant in 59% of the cases, showing a Kappa coefficient of 0.4, which corresponded to borderline agreement between fair and moderate. MRI tended to classify the cases as more advanced than the FIGO staging, principally in the case of stage I in which six out of seven patients were classified as stage II according to MRI findings. Ten cases were classified as stage IV and this finding would be clinically relevant considering that these patients have very poor prognoses [31].

In conclusion, MRI is highly valuable in predicting prognosis in cases of advanced cervical cancer, identifying factors that would not be available in clinical FIGO staging. Tumor volume immediately prior to the initiation of treatment was the most important predictive factor in this study, which is in agreement with reports available in the literature on this subject. Uterine body invasion was also a predictive factor. Evaluation of the tumor during and following treatment may succeed at earlier stages in detecting cases unresponsive to therapy. The RECIST report of complete response and partial response had no prognostic significance. Primary treatment can be adjusted based on MRI findings, and alternative treatment approaches can be tested for more aggressive and advanced cervical cancer and for those cases that are unresponsive to standard treatment.

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Table 1: Characteristics of the patients (n = 56)

Age: median (range)	51 years (23-75)	
MRI-1 tumor volume: median (range)	63.4 cm^3 (0.8 – 265.2)	
Histopathology	n	(%)
Squamous cell carcinoma	46	(82)
Adenocarcinoma	7	(13)
Adenosquamous carcinoma	1	(2)
Others	2	(4)
Clinical stage		
I	7	(12)
II	26	(46)
III	23	(4)
MRI-1 tumor volume		
< 50 cm^3	22	(39)
$\geq$ 50 cm^3	34	(61)
Uterine body invasion		
No	25	(45)
Yes	31	(55)
MRI-2 (RECIST)		
Complete response	20	(47)
Partial response	21	(49)
Stable disease	1	(2)
Disease Progression	1	(2)
Excluded	13	-
MRI-3 (RECIST)		
Complete response	33	(81)
Partial response	4	(10)
Disease Progression	4	(10)
Excluded or discontinued	15	-

MRI-1: magnetic resonance imaging carried out at staging.

MRI-2: magnetic resonance imaging carried out after concurrent chemoradiotherapy.

MRI-3: magnetic resonance imaging carried out 8-10 weeks after the end of treatment.

RECIST: Response Evaluation Criteria In Solid Tumors.

Table 2: Concordance between FIGO staging and MRI staging

MRI staging	FIGO staging				kappa (95%CI)
	I	II	III	Total	
	n (%)	n (%)	n (%)	n(%)	
I	1 (14)	2 (8)	0 (-)	3 (5)	
II	6 (86)	17 (65)	2 (9)	25 (45)	0.40 (0.26-0.53)
III	0 (-)	3 (12)	15 (65)	18 (32)	
IV	0 (-)	4 (15)	6 (26)	10 (18)	
Total	7 (13)	26 (46)	23 (41)	56 (100)	

FIGO – International Federation of Gynecology and Obstetrics.

MRI – Magnetic Resonance Imaging.

Table 3: Risk of death according to FIGO staging and MRI findings

Variable	Cox Hazard Ratio (95% CI)
Tumor volume (MRI-1)	
< $50cm^3$	1.00
≥ $50cm^3$	4.92 (1.09-22.12)
Uterine body invasion	
No	1.00
Yes	3.06 (0.94-9.89)
Response at MRI-2 (RECIST)	
Complete response	1.00
Partial response	1.15 (0.39-3.43)
Response at MRI-3 (RECIST)	
Complete response	1.00
Partial response	2.92 (0.59-14.61)
Disease Progression	81.18 (8.49-775.77)
FIGO staging and volume	
I/II and volume < $50cm^3$	1.00
I/II and volume ≥ $50cm^3$	8.83 (1.05-74.15)
III and volume < $50cm^3$	1.00
III and volume ≥ $50cm^3$	0.87 (0.10-7.31)
I/II - volume < $50cm^3$	1.00
III - volume < $50cm^3$	9.90 (0.59-165.01)
I/II - volume ≥ $50cm^3$	1.00
III - volume ≥ $50cm^3$	1.32 (0.43-4.10)
Tumor volume (MRI-1) adjusted according to FIGO staging	
Volume < $50cm^3$	1.00[1]
Volume ≥ $50cm^3$	4.09 (0.85-19.63)
FIGO staging adjusted according to tumor volume (MRI-1)	
I/II	1.00[1]
III	1.64 (0.55-4.90)

FIGO: International Federation of Gynecology and Obstetrics.

MRI-1: magnetic resonance imaging carried out at staging.

MRI-2: magnetic resonance imaging carried out after concurrent chemoradiotherapy.

MRI-3: magnetic resonance imaging carried out 8-10 weeks after the end of treatment.

RECIST: Response Evaluation Criteria In Solid Tumors.

[1] Cox Proportional Hazard Ratio

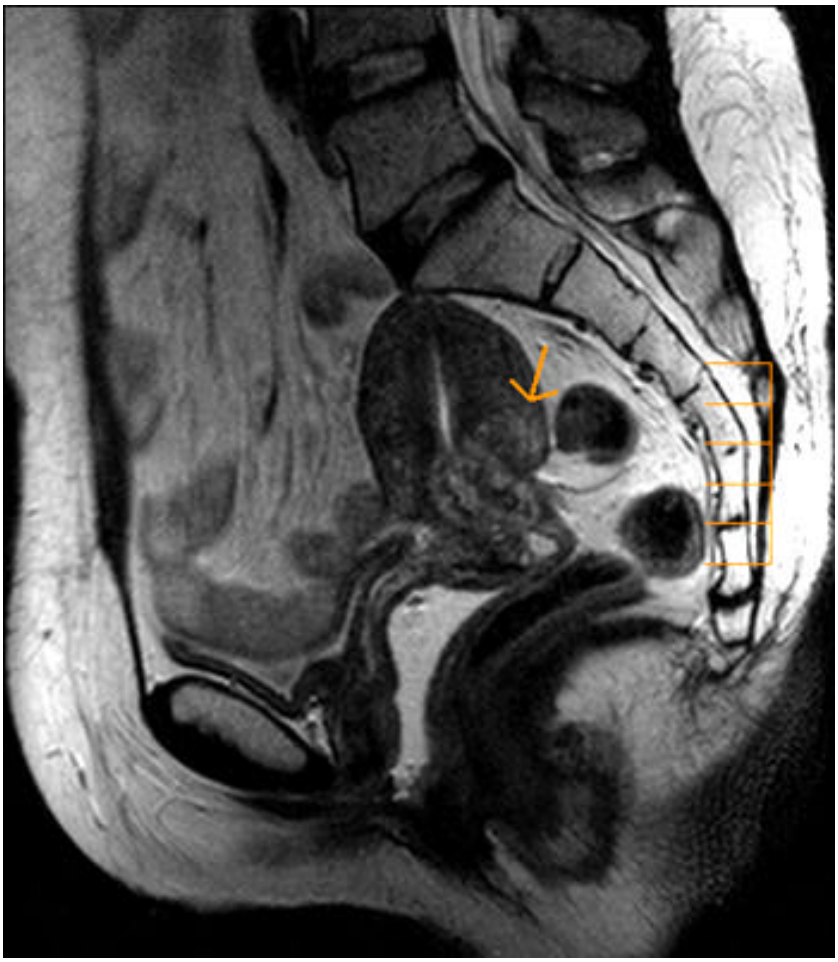

Figure 1: Uterine body invasion (arrow). T2-weighted TSE sequence in sagittal plane.

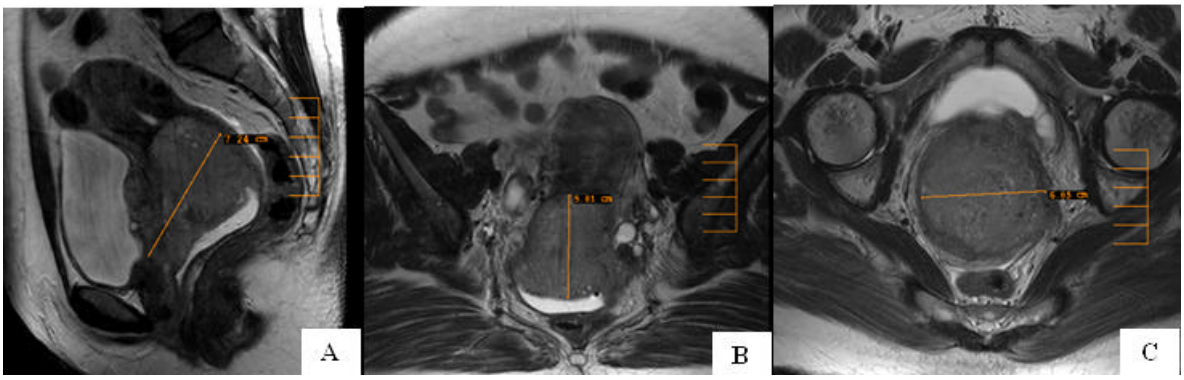

Figure 2: Measurement of tumor volume: A) Sagittal T2-weighted TSE image, tumor totally substituting the cervical stroma, measured at the greatest anteroposterior diameter. B) Coronal T2-weighted TSE image of the same patient showing the greatest craniocaudal diameter of the tumor. Note bilateral adenomegaly. C) Axial T2-weighted TSE image greatest laterolateral diameter of the tumor.

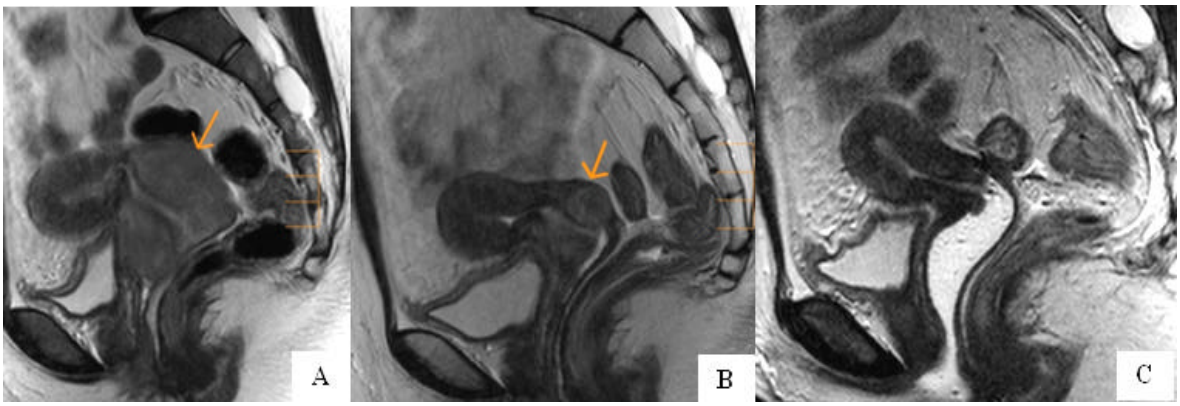

Figure 3: Serial magnetic resonance imaging of a stage IIIB patient. A) MRI at staging; B) MRI following concurrent chemotherapy showing partial response; C) MRI following brachytherapy showing complete response.

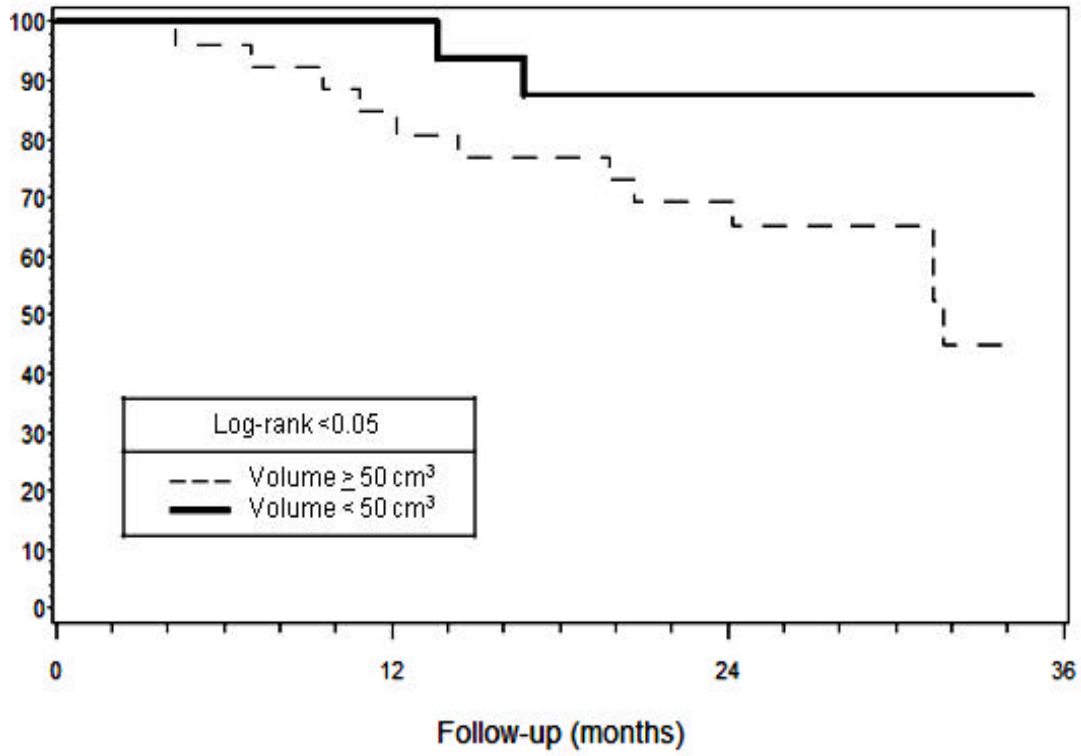

Figure 4: Overall survival curve stratified according to tumor volume.

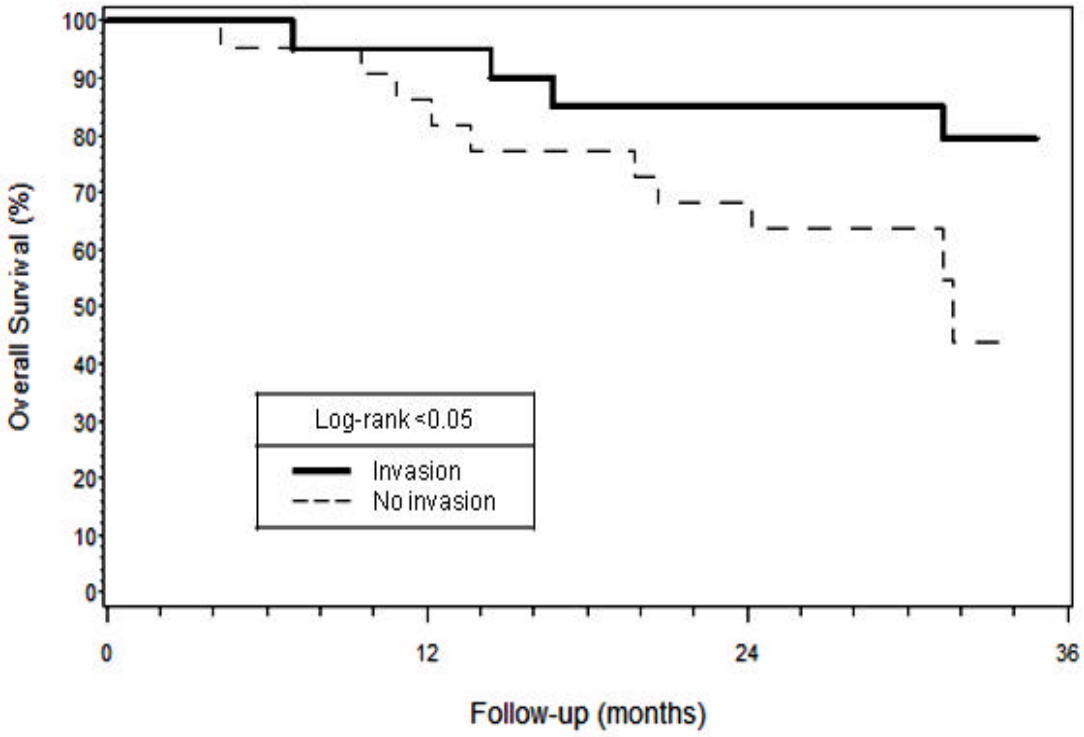

Figure 5: Overall survival stratified according to uterine body invasion.

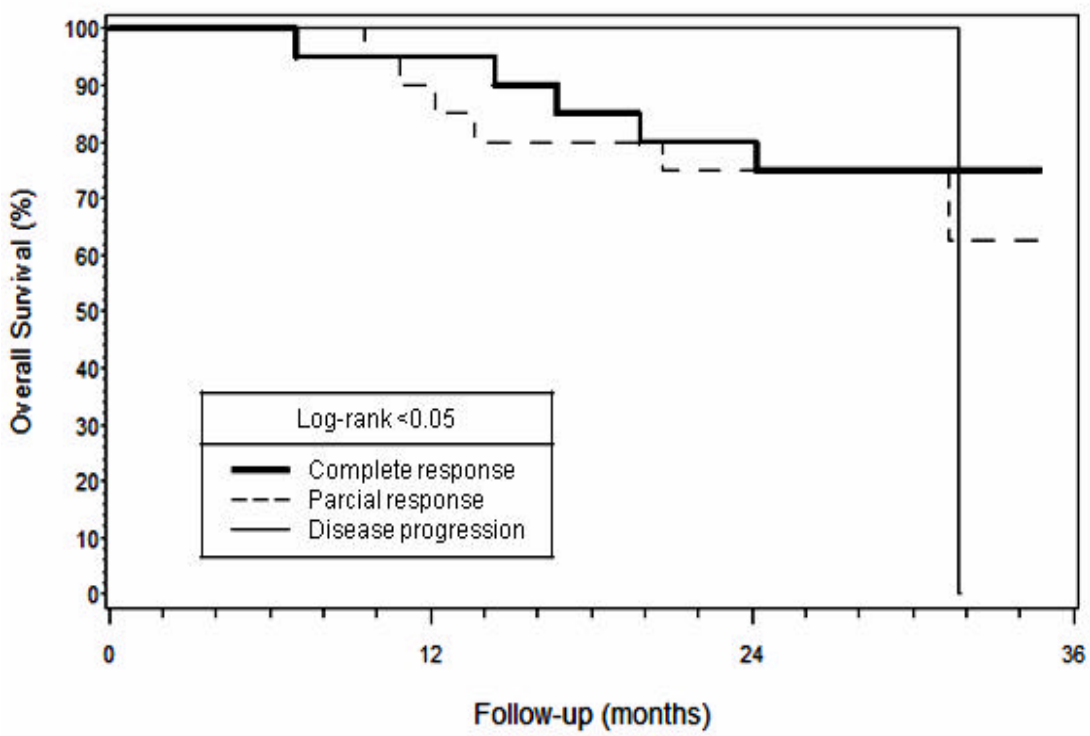

Figure 6: Overall survival stratified according to response to treatment at MRI carried out after concurrent chemoradiotherapy and before brachytherapy.

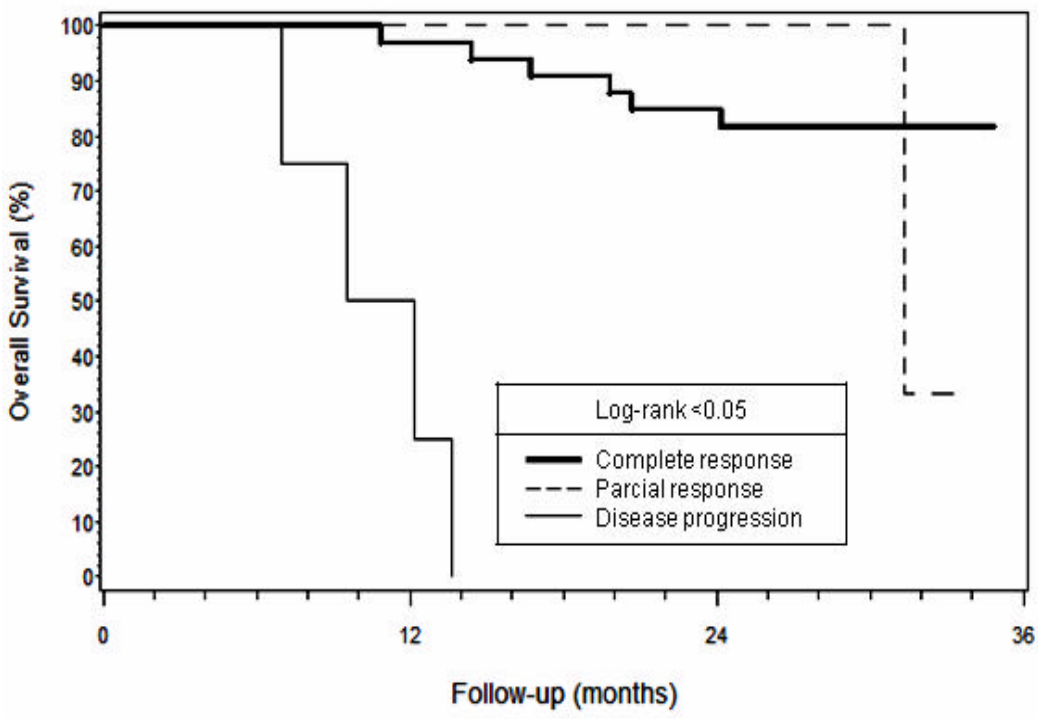

Figure 7: Overall survival stratified according to response to treatment at MRI carried out 8 weeks after brachytherapy.

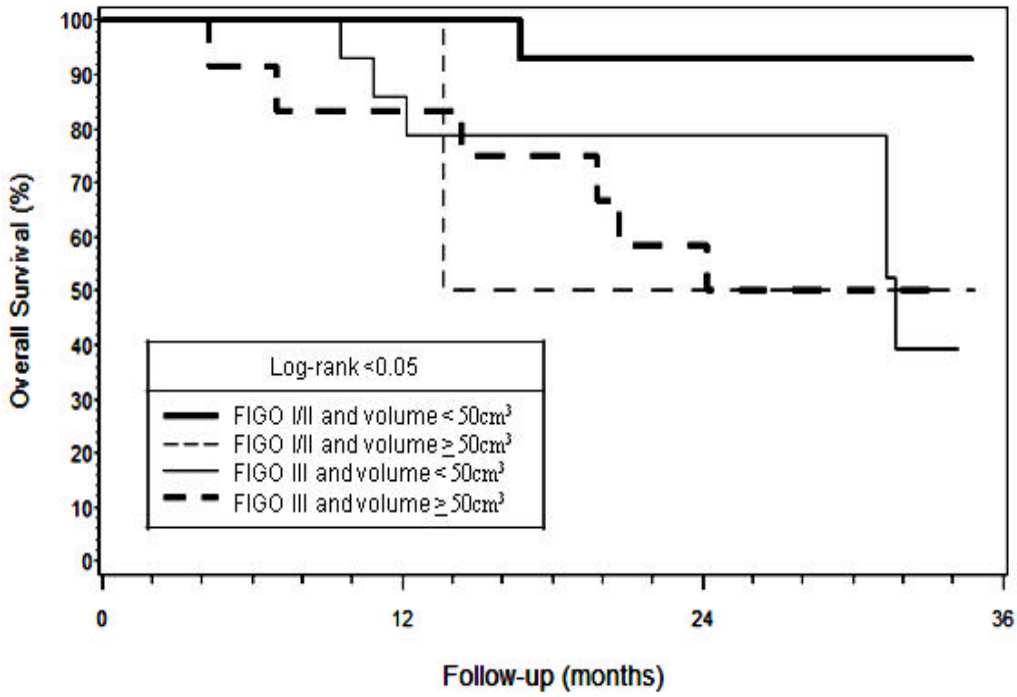

Figure 8: Overall survival stratified according to tumor volume and adjusted for staging.

4. Conclusões

1- A concordância entre o estadiamento clínico FIGO e o estadiamento utilizando as informações obtidas na RM pré-tratamento foi baixa.

2- O volume tumoral identificado pela RM no momento do estadiamento mostrou ser fator prognóstico significativo.

3- Na Ressonância realizada após o tratamento concomitante nenhuma das categorias de RECIST mostrou ter relevância prognóstica.

4- Na Ressonância realizada após a braquiterapia nenhuma das categorias do RECIST mostrou ter relevância prognóstica.

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6. Anexos

6.1. Anexo 1 – Response Evaluation Criteria in Solid Tumors (RECIST)

6.1.1. Eligibility

Only patient with measurable disease at baseline should be included in protocols where objective tumor tesponse is the primary endpoint.

Measurable disease – the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ?20 mm using conventional techniques or ?10 mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites,

pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.

– All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

– The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

– Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

6.1.2. Methods of Measurement

– CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

– Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

– When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

– The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

– Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

– Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

6.1.3. Baseline documentation of “Target” and “Non-Target” lesions

– All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.

– Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

– A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.

– All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.1.4. Response Criteria

6.1.4.1 Evaluation of target lesions

* Complete Response (**CR**):	Disappearance of all target lesions
* Partial Response (**PR**):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (**PD**):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
* Stable Disease (**SD**):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

6.1.4.2 Evaluation of non-target lesions

* Complete Response (**CR**):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (**SD**):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (**PD**):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

(1) Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

6.2. Anexo 2 – Ficha de Coleta de Dados

Nome:

Matrícula:

Paciente

|__|__|__|__|

Ficha de coleta de dados

Paciente

|__|__|__|__|

Idade:

Estadiamento Clínico Figo:_____

Mensuração clínica do tumor:_____cm

Extensão Clinica do tumor:

I__I Limitado a cervix
I__I Extensão para a vagina
I__I Extra-uterina
I__I Extensão para o corpo uterino
I__I 1/3 superior
I__I 1/3inferior
Orgão:_____

Estado Linfonodal Clínico:

I__I Não acometidos
I__I Acometido Cadeia Linfonodal:_____

Acometimento de Paramétrio:

I__I Não acometido
I__I Acometido
I__I Duvidoso
I__I Bilateral
I__I Direito
I__I Esquerdo

(1ª RM)

Volume Tumoral na RM: ____x____x____=_____ cm3

Acometimento Parametrial na RM:

I__I Não Acometido	I__I Bilateral
I__I Acometido	I__I Direito
I__I Duvidoso	I__I Esquerdo

Estado Linfonodal na RM:

I__I Não Acometido	I__I Bilateral
I__I Acometido	I__I Direito
	I__I Esquerdo

Cadeia linfonodal:_____

(2ª RM)

Tumor Residual: I__I Não
I__I Sim

Volume Tumoral na RM: _____x____x____=____cm3

Quimioterapia Combinada: Dose realizada:_____
Ciclos realizados:_____

Recidiva tumoral Clínica: Data:_____
Detectado através de:_____
Local:_____

Recidiva Tumoral na RM: Data:_____
Local:_____

Paciente

|__|__|__|__|

Lesão-Alvo – Primeira RM

Nº da lesão	Data do Exame	Localização	Medida (cm)
1.	___/___/___		__ __ __
2.	___/___/___		__ __ __
3.	___/___/___		__ __ __
4.	___/___/___		__ __ __
5.	___/___/___		__ __ __
6.	___/___/___		__ __ __
7.	___/___/___		__ __ __

Soma

_____cm

Paciente

|__|__|__|__|

Lesões Não-Alvo – Primeira RM

Nº da lesão	Data do Exame	Localização	Lesão Presente ou Ausente
1.	___/___/___		
2.	___/___/___		
3.	___/___/___		
4.	___/___/___		
5.	___/___/___		
6.	___/___/___		
7.	___/___/___		

Lesão
1= Presente – 2= Ausente – 3= Nova

Paciente

|__|__|__|__|

Lesão-Alvo –Segunda RM

Nº da lesão	Data do Exame	Localização	Medida (cm)
1.	___/___/___		__ __ __
2.	___/___/___		__ __ __
3.	___/___/___		__ __ __
4.	___/___/___		__ __ __
5.	___/___/___		__ __ __
6.	___/___/___		__ __ __
7.	___/___/___		__ __ __

Soma

_____cm

Paciente

|__|__|__|__|

Lesões Não-Alvo – Segunda RM

Nº da lesão	Data do Exame	Localização	Lesão Presente ou Ausente
1.	___/___/___		
2.	___/___/___		
3.	___/___/___		
4.	___/___/___		
5.	___/___/___		
6.	___/___/___		
7.	___/___/___		

Lesão
1= Presente – 2= Ausente – 3= Nova

Paciente

I__I__I__I__I

Resposta clínica RECIST

Data da avaliação da resposta ___/___/___ (_____ RM)

I__I Resposta Completa: I__I Resposta Parcial:

I__I Resposta Estável I__I Progressão da Doença

Soma total dos maiores diâmetros das lesões	Mudança absoluta em relação ao 1º estudo	Porcentagem de mudança em relação ao 1º exame

(**3ª RM)**

Braquiterapia data:
Data da RM:

Tumor Residual: I__I Não
I__I Sim

Volume Tumoral na RM: ____x____x____=_____ cm3

Recidiva tumoral Clínica: Data:_____
Detectado através de:_____
Local:_____

Recidiva Tumoral na RM: Data:_____
Local:_____

Paciente

|__|__|__|__|

Lesão-Alvo –Terceira RM

Nº da lesão	Data do Exame	Localização	Medida (cm)
1.	___/___/___		__ __ __
2.	___/___/___		__ __ __
3.	___/___/___		__ __ __
4.	___/___/___		__ __ __
5.	___/___/___		__ __ __
6.	___/___/___		__ __ __
7.	___/___/___		__ __ __

Soma

_____cm

Paciente

|__|__|__|__|

Lesões Não-Alvo – Terceira RM

Nº da lesão	Data do Exame	Localização	Lesão Presente ou Ausente
1.	___/___/___		
2.	___/___/___		
3.	___/___/___		
4.	___/___/___		
5.	___/___/___		
6.	___/___/___		
7.	___/___/___		

Lesão
1= Presente – 2= Ausente – 3= Nova

Paciente

|__|__|__|__|

Resposta clínica RECIST terceira RM

Data da avaliação da resposta ___/___/___ (_____ RM)

I__I Resposta Completa: I__I Resposta Parcial:

I__I Resposta Estável I__I Progressão da Doença

Soma total dos maiores diâmetros das lesões	Mudança absoluta em relação ao 1º estudo	Porcentagem de mudança em relação ao 1º exame

6.3. Anexo 3 – Distribuição das Mulheres Incluídas no Estudo

Número	Idade	Tipo histológico	Estadiamento FIGO	Estadiamento RM	Volume Tumoral	Resposta RM 2	Resposta RM 3
2088732	32	Carcinoma epidermóide	II A	IB1	18,67	RC	RC
2088831	47	Carcinoma epidermóide	II B	IVA	66,25	RP	RP
2088684	70	Carcinoma epidermóide	II B	IIB	24,96	RP	RC
2089090	23	Carcinoma epidermóide	II B	IIB	80,22	RP	PD
2088838	69	Carcinoma epidermóide	II B	IIB	16,86	RC	RC
2089204	40	Carcinoma epidermóide	III B	IIIB	32,76	RP	RC
2089161	52	Carcinoma epidermóide	III B	IIIB	64,35	RP	RC
2089554	28	Adenocarcinoma	II B	IB2	16,74	**	**
2089565	75	Outros	Ib 2	IB1	3,31	RC	RC
2089809	48	Outros	II B	IIIA	191,10	RP	PD
2089868	56	Carcinoma epidermóide	III B	IVA	78,65	RP	RC
2089888	53	Carcinoma epidermóide	II B	IVA	51,17	RP	RC
2089874	70	Carcinoma epidermóide	II B	IIB	221,09	PD	**
2089673	41	Carcinoma epidermóide	Ib 2	IIB	52,65	RP	RC
2089971	36	Adenocarcinoma	II B	IIB	41,60	RP	RC
2089922	43	Adenocarcinoma	II B	IIB	48,80	RP	RP
2089841	58	Carcinoma epidermóide	III B	IVA	224,64	DE	**
2089255	54	Carcinoma epidermóide	III B	IIIB	87,36	**	**
2089852	47	Adenocarcinoma	II B	IIB	78,65	RP	RP
2090099	36	Carcinoma epidermóide	II B	IIB	67,60	RP	RC
2090082	42	Carcinoma epidermóide	III B	IIIB	104,60	**	**
2089918	25	Carcinoma epidermóide	Ib1	IIB	13,65	RC	RC
2089717	51	Carcinoma epidermóide	Ib1	IIB	10,92	**	**
2089840	40	Adenocarcinoma	Ib1	IIB	36,86	RP	RC
2090136	47	Carcinoma epidermóide	III B	IIIA	265,20	RC	PD
2090137	38	Adenocarcinoma	II B	IIB	24,96	RC	RC
2090108	43	Carcinoma epidermóide	III B	IIIB	112,20	RC	RC
2090266	43	Carcinoma epidermóide	Ib2	IIB	42,12	RP	RC
2090178	64	Carcinoma epidermóide	III B	IIIB	62,40	RC	RC
2090217	37	Carcinoma epidermóide	III B	IIIA	71,50	RC	RC
2090312	69	Adenocarcinoma	III B	IVA	65,52	**	**
1243973	63	Carcinoma epidermóide	III B	IIIB	77,22	RC	RC
2090378	61	Carcinoma epidermóide	II B	IIB	20,97	RC	RC
2090421	42	Carcinoma epidermóide	II B	IIB	0,78	RC	RC
2090739	68	Carcinoma epidermóide	III B	IIB	41,60	**	**
2090795	66	Carcinoma epidermóide	III B	IIIB	100,81	**	**
2090757	65	Carcinoma epidermóide	III B	IIB	8,11	**	**
2090754	60	Carcinoma epidermóide	III B	IIIB	90,48	RC	RC
2090649	45	Carcinoma epidermóide	II B	IIIB	78,48	RP	RC
2090999	34	Carcinoma epidermóide	II B	IIIA	202,72	RP	RC
2090511	64	Carcinoma epidermóide	II B	IIB	8,67	**	**
2091102	33	Adenoescamoso	IB 2	IIA	51,84	RC	RC
2091090	40	Carcinoma epidermóide	III B	IIIB	151,19	RC	RC
2090873	66	Carcinoma epidermóide	II A	IVA	56,06	RP	RC
2091271	54	Carcinoma epidermóide	II B	IVA	67,60	RP	RC
2091221	71	Carcinoma epidermóide	III B	IVA	28,11	**	**
5001188	52	Carcinoma epidermóide	III B	IVA	120,12	RC	RC
5001416	58	Carcinoma epidermóide	II B	IIB	45,75	RC	RC
5001241	52	Carcinoma epidermóide	II B	IIB	56,16	**	**
2091276	60	Carcinoma epidermóide	II B	IIB	27,07	RC	RC
2090043	46	Carcinoma epidermóide	III B	IVA	203,84	RP	RP
5003266	57	Carcinoma epidermóide	IIB	IIB	174,72	RP	RC
2091189	49	Carcinoma epidermóide	IIB	IIB	121,68	**	**
5003794	27	Carcinoma epidermóide	IIIB	IIIB	130,13	**	**
5004121	51	Carcinoma epidermóide	IIIB	IIIB	46,80	RP	PD
5004668	52	Carcinoma epidermóide	IIIB	IIIB	222,30	RC	RC

6.4. Anexo 4 – Parecer do Comitê de Ética em Pesquisa

INCA

MINISTÉRIO DA SAÚDE
Comitê de Ética em Pesquisa-INCA

Rio de Janeiro, 27 de abril de 2005

Dra. Claudia Cristina Camisão
Pesquisadora Principal

Ref. Prot. **nº 02/05** – Ressonância Magnética na Mensuração da Resposta ao Tratamento Combinado de Quimioterapia e Radioterapia em Pacientes com Carcinoma de Colo Uterino Localmente Avançado

Prezada Doutora,

Informamos que o Comitê de Ética em Pesquisa do Instituto Nacional de Câncer após análise decidiu por **aprovar** o Protocolo intitulado: Ressonância Magnética na Mensuração da Resposta ao Tratamento Combinado de Quimioterapia e Radioterapia em Pacientes com Carcinoma de Colo Uterino Localmente Avançado em 15 de abril de 2005.

Estamos encaminhando a documentação pertinente para o CONEP, com vistas a registro e arquivamento.

Atenciosamente,

Dr. Luis Otávio Olivatto
Coordenador do Comitê de Ética em Pesquisa
CEP-INCA

CC: Dr. Reinaldo Rondineli
Diretor do H CII

INCA

MINISTÉRIO DA SAÚDE
Comitê de Ética em Pesquisa-INCA

Rio de Janeiro, 27 de abril de 2005

Dra. Claudia Cristina Camisão
Pesquisadora Principal

Ref. Prot. **nº 02/05** – Ressonância Magnética na Mensuração da Resposta ao Tratamento Combinado de Quimioterapia e Radioterapia em Pacientes com Carcinoma de Colo Uterino Localmente Avançado

Prezada Doutora,

Informamos abaixo a composição do Comitê de Ética em Pesquisa do Instituto Nacional de Câncer que analisou e aprovou o estudo acima especificado.

Dra. Adriana Alves de Souza Scheliga	Médica Oncologista Clínica – H CI
Dra. Adriana Bonomo	Médica
Dr. André Marcelo Machado Soares	Teólogo / Filósofo – Extra – INCA
Dr. Cláudio Calazan do Carmo	Médico Oncologista Clínico H – CII
Dr. Carlos Frederico de Freitas Lima	Médico Cirurgião Mastologista - H CIII
Sra. Dinah Schumer	Representante de Usuários – Extra –INCA
Profa. Fátima Bayma	Administração Pública – FGV – Extra - INCA
Dr. Luis Otávio Olivatto	Oncologista - Coordenador do CEP
Dr. Marcelo Ribeiro Schirmer	Médico Infectologista – INCA – Substituto do Presidente
Enfª Vânia Maria Fernandes Teixeira	Enfermeira INCA

Atenciosamente

Dr. Luis Otávio Olivatto
Coordenador do Comitê de Ética em Pesquisa
CEP-INCA