Daniel Grossi Marconi

VIABILIDADE DA UTILIZAÇÃO DE RNM-DIFUSÃO COMO PREDITOR PROGNÓSTICO EM PACIENTES COM CÂNCER DE COLO UTERINO: UM ESTUDO RETROSPECTIVO

Tese apresentada ao Programa de Pós-Graduação da Fundação Pio XII – Hospital de Câncer de Barretos para obtenção de título de Doutor em Oncologia.

Área de Concentração: Oncologia

Orientador: José Humberto Tavares Guerreiro Fregnani

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Os pesquisadores declaram não ter qualquer tipo de conflito de interesse relacionado a este estudo.

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“Eu guardei muitas coisas em minhas mãos, e perdi todas; mas todas as que coloquei nas mãos de Deus, essas eu ainda possuo.”

Marthin Luther King

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LISTA DE ABREVIATURAS – INTRODUÇÃO E DISCUSSÃO

18-FDG	18-FluorDesoxiGlicose
AP	Antero-Posterior
CC	Cranio-Caudal
CDA	Coeficiente de Difusão Aparente
CDA_{Desvio}	Coeficiente de Difusão Aparente – valor do desvio
$CDA_{máx}$	Coeficiente de Difusão Aparente – valor máximo
$CDA_{méd}$	Coeficiente de Difusão Aparente – valor médio
$CDA_{mín}$	Coeficiente de Difusão Aparente – valor mínimo
CEC	Carcinoma escamocelular
EQD2	Equivalente de Dose em Fração de 2-Gray
FIGO	Federação Internacional de Ginecologia e Obstetrícia
Gy	Gray
HPV	*Human Papilomavirus* (Papiloma Vírus Humano)
LL	Latero-Lateral
LND	Linfonodo
PET	*Positron Emission Tomography* (Tomografia por Emissão de Pósitron)
QT	Quimioterapia
RC	Resposta Completa
RI	Região de Interesse

RNC Resposta Não-Completa

RNM Ressonância Nuclear Magnética

RNMd Ressonância Nuclear Magnética – sequência de difusão

SUV *Standardized Uptake Value* (Valor Padronizado de Captação)

SUV_{max} *Standardized Uptake Value – Maximmun Value* (Valor Máximo Padronizado de Captação)

LISTA DE ABREVIATURAS – ARTIGO CIENTÍFICO

ADC_{dev} *Apparent Diffusion Coefficient – deviation value* (Coeficiente de Difusão Aparente – Desvio Padrão)

ADC_{max} *Apparent Diffusion Coefficient – maximum value* (Coeficiente de Difusão Aparente – Valor Máximo)

ADC_{mean} *Apparent Diffusion Coefficient – mean value* (Coeficiente de Difusão Aparente – Valor Médio)

ADC_{min} *Apparent Diffusion Coefficient – minimum value* (Coeficiente de Difusão Aparente – Valor Mínimo)

AP *Anterior to Posterior* (Anterior para Posterior)

CC *Cranial to Caudal* (Cranial para Caudal)

CC *Cubic Centimeter* (Centímetros Cúbicos)

CH *Chemotherapy* (Quimioterapia)

CR	*Complete Response* (Resposta Completa)
CT	*Computed Tomography* (Tomografia Computadorizada)
DFS	*Disease Free Survival* (Sobrevida Livre de Doença)
DSS	*Disease Specific Survival* (Sobrevida Doença-Específica)
DW	*Diffusion Weighted* (Ponderação em Difusão)
DWI	*Diffusion Weighted Image* (Imagem Ponderada em Difusão)
EBRT	*External Beam Radiation Therapy* (Radioterapia Externa ou Teleterapia)
EQD2	*Dose Equivalent in Gy-2* (Equivalente de Dose em Fração de 2-Gray)
FOV	*Field of View* (Campo de Visão)
FU	*Follow Up* (Seguimento)
GTV	*Gross Tumor Volume* (Volume Tumoral Grosseiro)
HDR	*High Dose Rate* (Alta Taxa de Dose)
HPV	*Human Papilomavirus* (Papiloma Vírus Humano)
LN	*Lymph Node* (Linfonodo)
LR	*Left to Right* (Esquerda para Direita)
LRC	*Local Regional Control* (Controle Locorregional)
MRI	*Magnetic Ressonance Image* (Ressonância Nuclear Magnética)
N-	*Negative Nodes* (Linfonodos Negativos)
N+	*Positive Nodes* (Linfonodos Positivos)
NCR	*Non-Complete Response* (Resposta Não-Completa)

PET *Positron Emission Tomography* (Tomografia por Emissão de Pósitron)

RECIST *Response Evaluation Criteria In Solid Tumors* (Critérios de Avaliação de Resposta em Tumores Sólidos)

ROC *Receiver Operating Characteristic* (Característica de Operação do Receptor)

ROI *Region of Interest* (Região de Interesse)

RT *Radiation Therapy* (Radioterapia)

SCC *Squamous Cell Carcinoma* (Carcinoma Escamocelular)

SUV *Standardized Uptake Value* (Valor Padronizado de Captação)

SUV_{max} *Standardized Uptake Value – Maximmun Value* (Valor Máximo Padronizado de Captação)

LISTA DE SÍMBOLOS

%	Porcentagem
=	Igual
≥	Maior ou igual
≤	Menor ou igual
®	Marca registrada
T	Tesla
Gy	Gray

RESUMO

Marconi, DG. *Viabilidade Da Utilização De Rnm-Difusão Como Preditor Prognóstico Em Pacientes Com Câncer De Colo Uterino: Um Estudo Retrospectivo*. **Tese (Doutorado)** – Barretos: Hospital De Câncer De Barretos; 2016.

OBJETIVO: Investigar a associação de parâmetros da sequência de difusão da Ressonância Nuclear Magnética (RNMd) pré-tratamento com variáveis de estadiamento e desfechos clínicos (Controle Loco-Regional – CLR; Sobrevida Livre de Doença – SLD; Sobrevida Câncer Específica – SCE) em mulheres com câncer de colo de útero submetidas a radio-quimioterapia definitiva. **PACIENTES E MÉTODOS**: Foram analisados, de forma retrospectiva, dados de 66 pacientes com câncer cervical tratadas com radio-quimioterapia definitiva que possuíam uma RNM pré-tratamento com sequência ponderada em difusão entre 2012-2013 no Hospital de Câncer de Barretos. As regiões de interesse (RI) foram desenhadas manualmente por um de três diferentes radiologistas com experiência em anatomia pélvica, em um único corte central, englobando a maior área tumoral, com exclusão das áreas de necrose. Valores de Coeficiente de Difusão Aparente (CDA) mínimo, médio, máximo e do desvio padrão ($x10^{-3}mm^2/s$) foram extraídos para cada RI. Curvas ROC foram construídas para a escolha do ponto de corte ideal para cada variável de CDA. Foi utilizado o teste de Mann Whitney para comparar valores de CDA com características clínicas e de estadiamento. Utilizou-se o modelo confirmatório para a análise múltipla dos dados (modelo ajustado pela volumetria tumoral para CLR e pelo estadiamento da FIGO para SLD e SCE). Curvas de Kaplan Meyer foram construídas para SLD e SCE. A idade mediana das mulheres ao diagnóstico foi de 52 anos. Dois terços delas tinham doença nos estádios I e II e as demais, nos estádios III e IV. Histologia escamosa foi evidenciada em 82% dos casos, sendo que 88% das pacientes receberam quimioterapia concomitante à radioterapia. O equivalente de dose em Gy-2 do tratamento combinado de teleterapia e braquiterapia foi de 82.2 Gy (74-84). **RESULTADOS**: Mulheres com doença nos estádios III e IV tiveram valores médios de $CDA_{máx}$ (Desvio Padrão – DP) significativamente maiores quando comparadas com aquelas com doença nos estádios iniciais ($1{,}806$ $(0{,}4)$ vs $1{,}485$ $(0{,}4)$; $p=0{,}01$). Pacientes com linfonodos radiologicamente suspeitos tiveram valores médios de $CDA_{máx}$ (DP)

significativamente mais altos que as mulheres sem linfonodo suspeito (1,995 (0,3) vs 1551 (0,5); p=0,03). Após seguimento mediano de 32 meses (5-43), 11 pacientes (17%) apresentaram doença recorrente e 8 (12%) tiveram morte por causa do câncer. Os valores de corte determinados pela curva ROC foram: 0,488 ($CDA_{mín}$); 0,827 ($CDA_{méd}$); 1,838 ($CDA_{máx}$); 0,148 (CDA_{Desvio}). Valores de $CDA_{mín}$ maiores que o ponto de corte associaram-se a taxas significativamente menores de SLD (HR = 3,632 – IC: 1,094-12,054; p=0,035) e SCE (HR = 4,401 – IC: 1,048-18,483; p=0,043). **CONCLUSÃO**: Valores de $CDA_{máx}$ aferidos no tumor primário podem estar associados ao estadiamento FIGO e ao *status* linfonodal. $CDA_{mín}$ pode ser um fator prognóstico associado a SLD e SCE em pacientes com câncer de colo de útero tratadas com radio-quimioterapia. Validação prospectiva destes dados está em curso atualmente.

PALAVRAS-CHAVE: Neoplasia Uterina, Imagem Multimodal, Imagem por Ressonância Magnética, Difusão, Imagem de difusão por ressonância magnética.

ABSTRACT

Marconi, DG. *Viability Of Using MRI - Diffusion As A Predictor Of Prognosis In Patients With Cervical Cancer: A Retrospective Study*. **Thesis (Ph.D.)** - Barretos : Cancer Hospital In Barretos; 2016.

PURPOSE: To investigate the association of pre-treatment Diffusion Weighted (DW) Magnetic Resonance Imaging (MRI) parameters with baseline clinical features and clinical outcomes (local regional control (LRC), disease free survival (DFS) and disease specific survival (DSS)) in cervical cancer women treated with definitive chemoradiation. **METHODS AND MATERIALS:** The retrospective analysis was performed on 66 women with cervical cancer treated with definitive chemoradiation who underwent pre-treatment diffusion weighted imaging-MRI at Barretos Cancer Hospital between 2012-2013. A region of interest (ROI) was manually drawn by one of three radiologists with experience in pelvic imaging on a single axial CT slice encompassing the widest diameter of the cervical tumor while excluding areas of necrosis. The following apparent diffusion coefficient (ADC) values ($x10^{-3}$ mm^2/s) were extracted for each ROI: Minimum - ADC_{min}, Maximum - ADC_{max}, Mean - ADC_{mean}, and Standard Deviation of the ADC - ADC_{dev}. Receiver operating characteristic (ROC) curves were built to choose the most accurate cut off value for each ADC value. Correlation between imaging metrics and baseline clinical features were evaluated using the Mann Whitney test. Confirmatory multi-variate Cox modeling was used to test associations with LRC (adjusted by gross tumor volume – GTV), DFS and DSS (both adjusted by FIGO stage). Kaplan Meyer curves were built for DFS and DSS. Women median age was 52 years (range 23-90). Two thirds had FIGO stage I-II disease while one third had FIGO stage III-IV disease. 82% had squamous cell cancer and 88% received concurrent cisplatin chemotherapy with radiation. Median EQD2 of external beam and brachytherapy was 82.2 Gy (range 74-84). **RESULTS:** Women with disease staged III-IV (FIGO) had significantly higher mean ADC_{max} values compared with those with disease staged I-II (1.806 (0.4) vs 1.485 (0.4), p=0.01). Patients with imaging defined positive nodes also had significantly higher mean (±SD) ADC_{max} values compared with lymph node negative patients (1.995 (0.3) vs 1.551 (0.5), p=0.03). With a median follow-up of 32 months (range 5-43) 11 patients (17%) have

developed recurrent disease and 8 (12%) have died because of cervical cancer. ROC curves showed optimal cutoffs for ADC_{min} (0.488×10^{-3}), ADC_{mean} (0.827×10^{-3}), ADC_{max} (1.838×10^{-3}) and ADC_{dev} (0.148×10^{-3}). ADC_{min} higher than the cutoff was significantly associated with worse DFS (HR = 3.632 – 95% CI: 1.094-12.054; p = 0.035) and DSS (HR = 4.401 – 95% CI: 1.048-18.483; p = 0.043). **CONCLUSION:** Pre-treatment ADC_{max} measured in the primary tumor may be associated with FIGO stage and lymph node status. Pre-treatment ADC_{min} may be a prognostic factor associated with disease-free survival and disease-specific survival in cervical cancer patients treated with definitive chemoradiation. Prospective validation of these findings is currently ongoing.

KEYWORDS: Uterine Cervical Neoplasms, Multimodal Imaging, Magnetic Resonance Imaging, Diffusion Weighted MRI, Functional MRI.

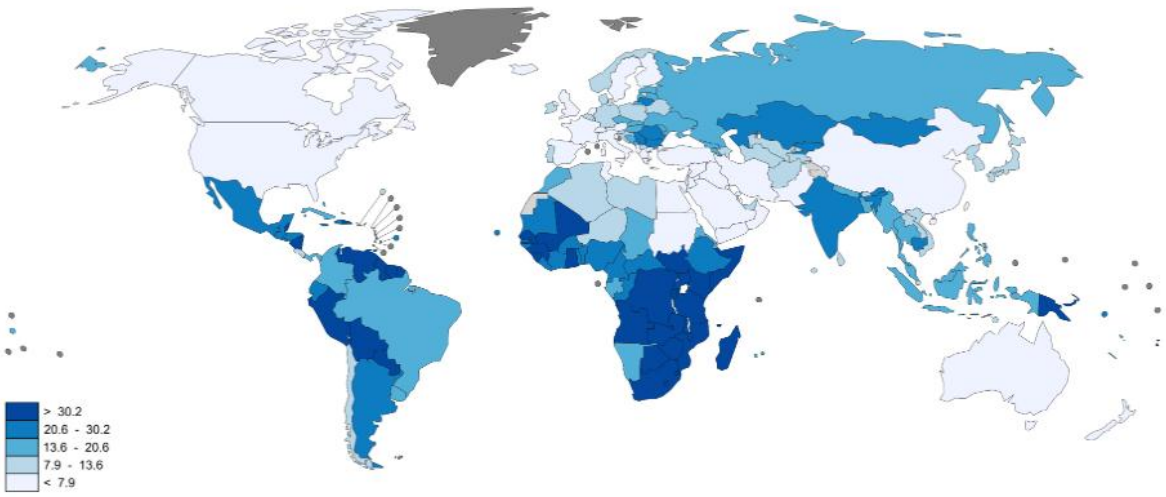
1. INTRODUÇÃO

1.1 Câncer de Colo de Útero

O câncer cervical é uma doença global[1], com estimativa de mais de 500.000 novos casos diagnosticados por ano. A Agência Internacional de Pesquisa em Câncer (IARC)[2] estima cerca de 528 mil novos casos por ano, com aproximadamente 266.000 mortes anuais (Figuras 1, 2 e 3).

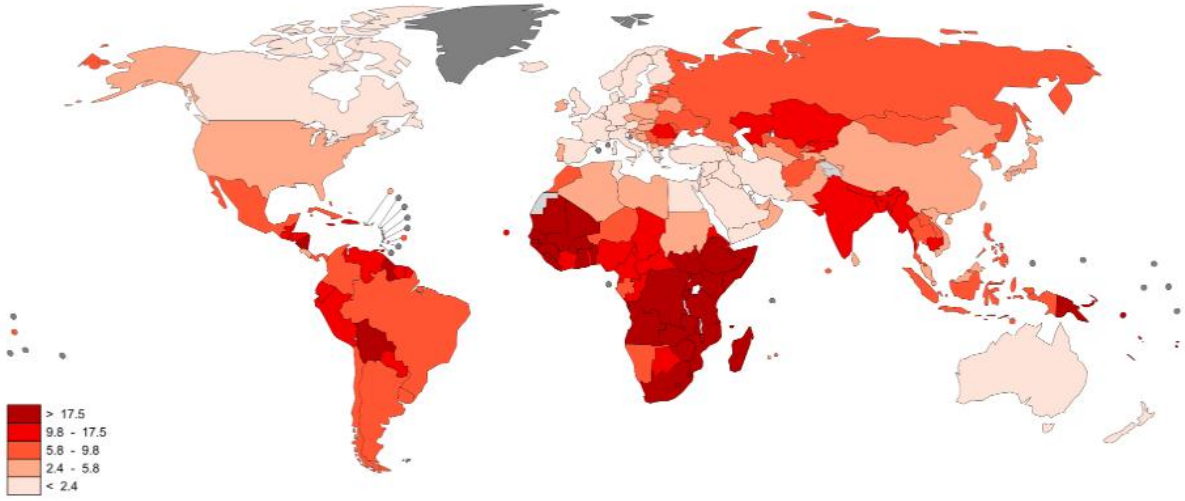
Nos países desenvolvidos, representa 4,2% de todos os tumores do sexo feminino[3]. A maioria dos casos (cerca de 87%) ocorre nos países em desenvolvimento, principalmente por causa da precariedade dos programas de rastreamento[2]. No Brasil, é o terceiro tumor mais frequente na população feminina, estando atrás apenas do câncer de mama e do câncer colorretal[4].

No Brasil, a incidência estimada para o ano de 2016 é de 16.340, com risco estimado de 15,85 casos a cada 100.000 mulheres. Quando se regionaliza a incidência, observa-se que há uma correlação inversa com o nível de desenvolvimento socioeconômico (desconsiderando câncer de pele não melanoma): na região Norte, o câncer de colo uterino é o mais incidente (23,97 / 100.000 mulheres); nas regiões Centro-Oeste (20,72 / 100.000 mulheres) e Nordeste (19,49 / 100.000 mulheres) é o segundo mais incidente; na região Sudeste (11,30 / 100.000 mulheres), o quarto e na região Sul (15,17 / 100.000 mulheres), o quinto mais incidente[5]. A figura 4 mostra a incidência do câncer de colo de útero em relação aos demais tipos de câncer na população feminina no Brasil.



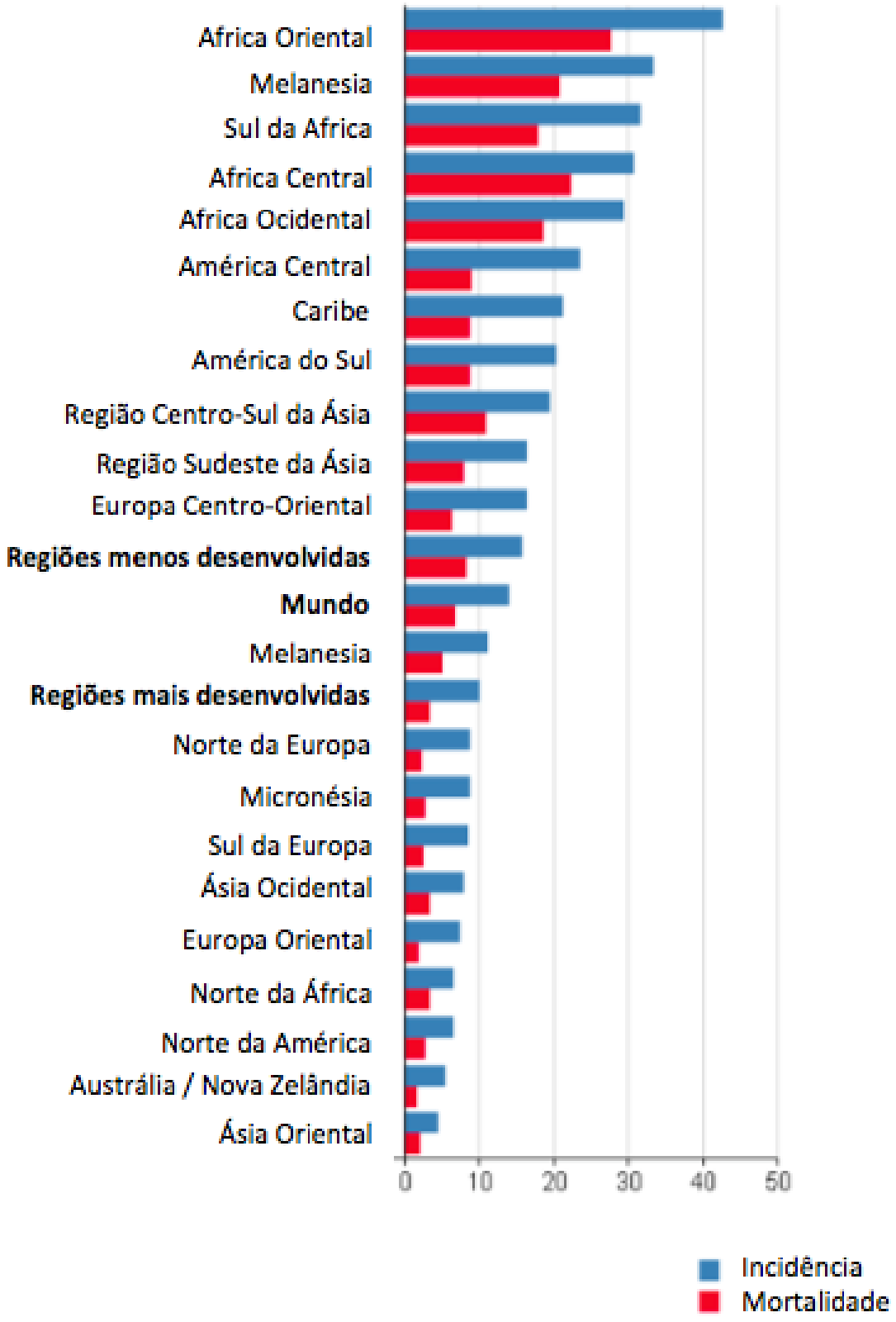
Fonte: Globocan[2].

Figura 1 Incidência estimada de câncer de colo de útero no mundo.



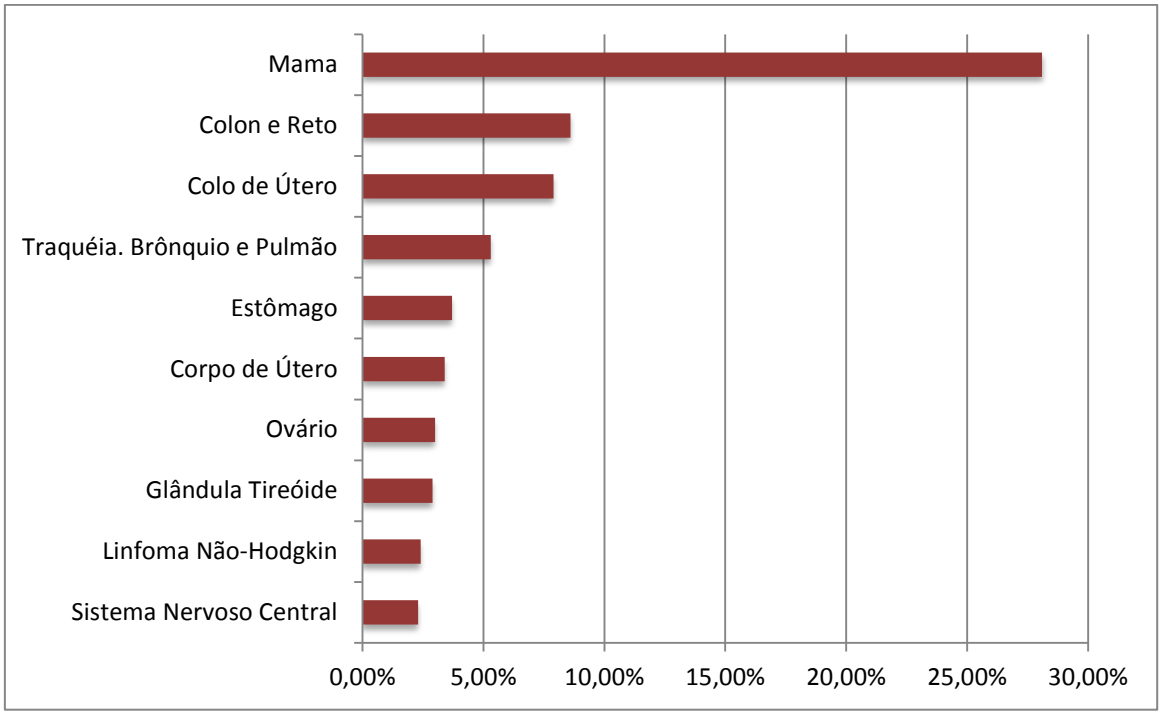
Fonte: Globocan[2].

Figura 2 Mortalidade estimada de câncer de colo de útero no mundo.



Fonte: Globocan[2].

Figura 3 Taxas estimadas de incidência e mortalidade por câncer de colo de útero em diversos lugares do mundo.



Fonte: Instituto Nacional do Câncer[5]

Figura 4 Incidência de neoplasias (exceto câncer de pele não melanoma) na população feminina brasileira.

Apesar dos altos coeficientes, tanto a incidência quanto a mortalidade tem sofrido redução ao longo das últimas décadas nos países desenvolvidos, graças principalmente às políticas de prevenção e rastreamento na Europa Ocidental, Estados Unidos, Canadá, Nova Zelândia, China e Japão[6].

1.2 Relação com o HPV

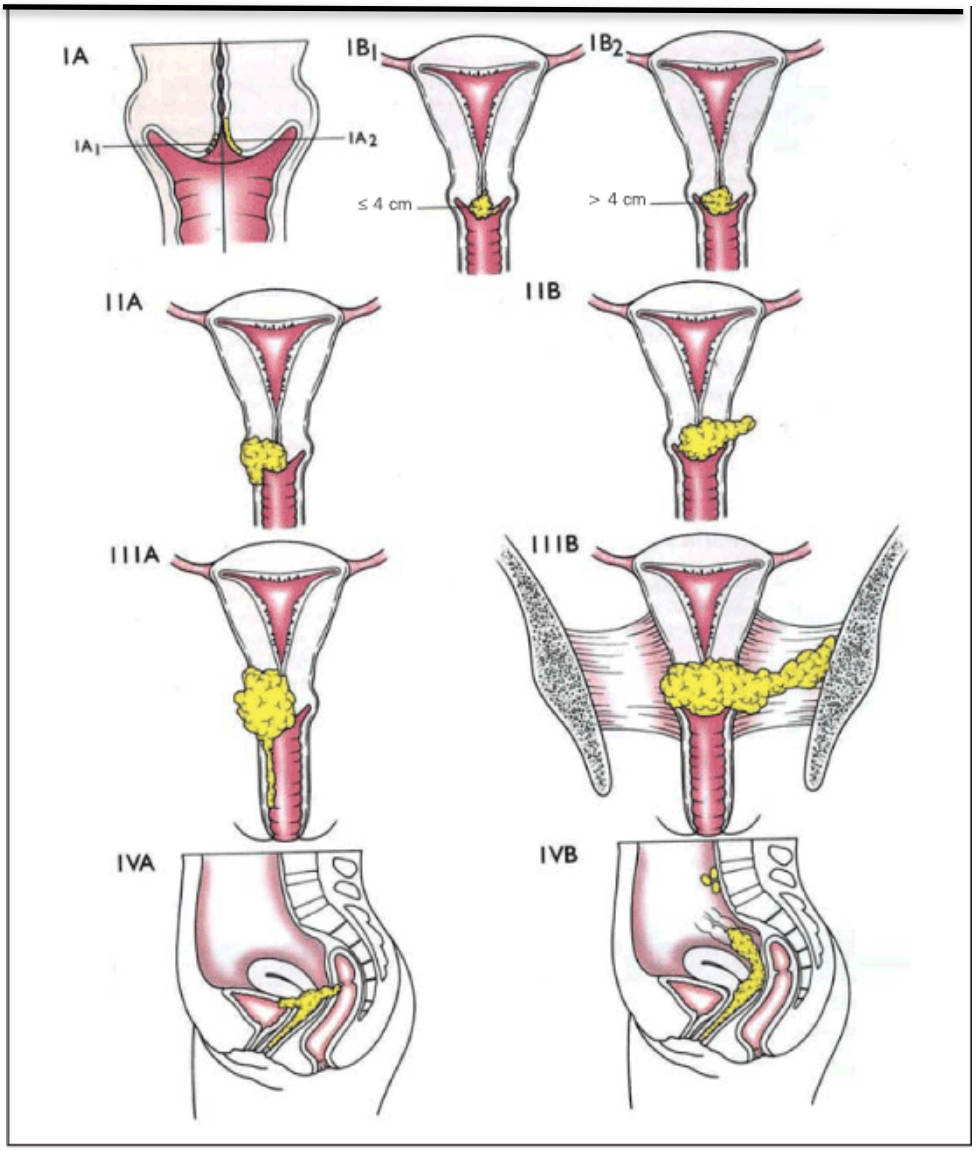
Entre os principais fatores relacionados à gênese da doença, o HPV é o mais importante. Historicamente, desde 1949, quando o exame de citologia cervical foi proposto pelo patologista Papanicolaou (George) para o rastreio de lesões precursoras, notou-se correlação direta entre a atividade sexual e o surgimento do câncer de colo uterino[7]. Com o surgimento de estudos multicêntricos que confirmaram a presença de DNA do HPV em quase 100% dos carcinomas invasores[8,9], o mundo praticamente adotou a idéia de que o HPV é causa necessária para o desenvolvimento do câncer colo uterino[10].

Entretanto, como apenas uma parte das mulheres infectadas pelo HPV desenvolve a doença, concluiu-se que o vírus seria uma condição necessária, mas não suficiente para o desenvolvimento do câncer de colo do útero[9,11,12].

Há diferentes tipos de Papiloma Vírus que infectam o ser humano, tendo sido descritos mais de uma centena deles[13,14]. Em termos de risco para o desenvolvimento da neoplasia, eles foram classificados em 2003 por Munoz et al.[13, 14] como de baixo (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, e CP6108, sendo os tipos 34, 57 e 83 classificados como indeterminados) e alto risco (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, e 58, sendo que o 26, 53 e 66 também seriam provavelmente classificados como de alto risco).

1.3 Estadiamento

O estadiamento do câncer do colo do útero é fundamentalmente clínico, sendo o sistema proposto pela Federação Internacional de Ginecologia e Obstetrícia[15] (FIGO) o mais utilizado. Para essa classificação, o armamentário é basicamente clínico (palpação, inspeção, colposcopia, curetagem endocervical, histeroscopia, cistoscopia, proctoscopia, urografia intravenosa e RX para investigação do pulmão e esqueleto), e os exames devem ser realizados previamente à instituição de qualquer tipo de tratamento. A figura 5 esquematiza o estadiamento pela FIGO.



Fonte: Camisão et al.[16]

Figura 5 Estadiamento FIGO (AJCC 7a Edição)[101]

Descrição:

IA1: < 3 mm de profundidade e < 7 mm de largura;

IA2: 3-5 mm de profundidade e < 7 mm de largura;

IB1: Tumor < 4 cm;

IB2: Tumor > 4 cm;

IIA1: Tumor < 4 cm com invasão de vagina (exceto parte inferior);

IIA2: Tumor > 4 cm com invasão de vagina (exceto parte inferior);

IIB: Tumor invade tecidos ao redor do colo;

IIIA: Tumor invade 1/3 inferior da vagina;

IIIB: Tumor invade tecidos pélvicos com bloqueio de um ou ambos uréteres ou disseminação para linfonodos pélvicos;

IVA: Tumor invade bexiga ou reto;

IVB: Tumor se disseminou para linfonodos não-pélvicos ou órgãos distantes.

Deve-se atentar para o fato de que adição de exames complementares, como a tomografia computadorizada e a ressonância nuclear magnética, podem auxiliar na estratégia terapêutica e, por vezes , até fornecer informações prognósticas, mas não devem alterar a classificação clínica (estadiamento) uma vez que esses exames não são universalmente difundidos, principalmente nos países com poucos recursos econômicos.

1.4 Tratamento

1.4.1 Carcinoma in situ e estádio IA1:

Como a disseminação linfonodal e a recorrência em caso de margens negativas à conização são virtualmente 0%, apenas a conização – ou mesmo a histerectomia simples – podem ser consideradas suficientes. Alternativamente, laserterapia ou crioterapia podem ser usados em alguns casos selecionados[17].

Quando a profundidade de invasão do carcinoma na cérvix for menor que 3 mm e quando não houver invasão angiolinfática, a taxa de disseminação linfonodal é menor que 1%, sendo adequada a histerectomia simples sem linfadenectomia (e ooforectomia opcional). Entretanto, pode-se considerar a conização ou a traquelectomia nas pacientes ainda sem prole constituída[17]. Quando um desses fatores está presente, ou seja, quando há invasão angiolinfática ou profundidade de invasão maior do 3mm, a disseminação linfonodal ou a recorrência aumentam para taxas que variam de 2 a 13%[18,19], o que determina a necessidade de procedimentos mais radiciais do ponto de vista oncológico.

Terapias cirúrgicas são, assim, preferidas nos casos de doença em fase inicial. Nos casos inoperáveis, a radioterapia é uma opção viável, com resultados comparáveis à cirurgia[20].

1.4.2 Estádios IA2 / IB1 / IIA1 (< ou = 4 cm)

Essas lesões podem ser tratadas tanto com cirurgia como com radioterapia. A decisão passa, invariavelmente, pela avaliação de efeitos colaterais e complicações de ambos os tratamentos, levando-se em consideração a condição clínica da paciente[17].

A cirurgia padrão para esses casos é a histerectomia radical com linfadenectomia pélvica e, em alguns casos, para-aórtica. Com essa abordagem, a sobrevida livre de doença em 5 anos varia de 80-92%[21, 22], números estes bastante similares aos encontrados nas séries de radioterapia exclusiva[23-25].

1.4.3 Estádios IB2 / IIA2 (> 4 cm) - Lesões do tipo Bulky (não candidatas a cirurgia) / Estádios IIB-IVA

O tratamento padrão dos casos localmente avançados é a radioterapia associada à quimioterapia concomitante, especialmente após uma série de estudos publicados no final da década de 1990[26-28].

Para as lesões do tipo *bulky*, ou seja, aquelas com diâmetro maior do que 4 cm, é necessário fazer um curso de radioterapia externa para que a redução tumoral permita uma melhor conformação anatômica da disposição dos aplicadores de braquiterapia[17].

1.5 Avaliação de Resposta ao Tratamento

Sabe-se que a identificação precoce de marcadores preditivos e prognósticos durante o tratamento permitiria o desenvolvimento de uma estratégia resposta-adaptada, o que poderia melhorar os resultados clínicos. Isto se faz ainda mais importante numa doença como o câncer de colo uterino, cujos casos localmente avançados tratados de maneira definitiva com radio-quimioterapia apresentam uma taxa de doença persistente ou recorrente de 20 a 40%.

Nesse contexto, não se pode deixar de definir o conceito de marcador biológico, termo usado pela primeira vez em 1980[29] e que é definido como uma medida laboratorial ou

clínica que reflete a atividade de uma doença[30]. Existem vários marcadores identificados para muitas doenças como, por exemplo, do sistema nervoso central, em que medidas de ressonância nuclear magnética são usadas para avaliar o tratamento da Esclerose Múltipla e Doença de Alzheimer; tomografia com emissão de pósitron (PET*, positron emission tomography*), com transportadores de dopamina na Doença de Parkinson, entre outros[31-34]. Praticamente em todos os casos esses marcadores se correlacionam quantitativamente (direta ou indiretamente) com a progressão da doença.

Nessa mesma linha, um marcador substituto (*surrogate marker*), termo usado pela primeira vez em 1988[35], pode ser definido como uma medida laboratorial ou sinal físico que é usado em estudos científicos terapêuticos como substituto para um desfecho clinico significativo – por exemplo, sobrevida[36]. A diferença primordial entre um biomarcador e um marcador substituto é que o biomarcador é um candidato a marcador substituto, enquanto um marcador substituto é um teste usado como medida dos efeitos de um determinado tratamento[30].

Um dos biomarcadores utilizados no câncer colouterino é o SUV (*Standardized Uptake Value*), que é a medida quantitativa do PET e que reflete a avidez celular por glicose e, assim, o metabolismo e a atividade celular. Entretanto, o dispêndio da implantação e realização rotineira deste exame o torna financeiramente inviável para muitos centros, especialmente sem a realização de um pormenorizado estudo de custos[37]. O resultado disso é que, no Brasil, entre as esferas pública e privada, há pouco mais de 100 aparelhos em funcionamento[38], o que resulta numa proporção de um aparelho para cada dois milhões de habitantes (o preconizado pela Organização Mundial da Saúde é um aparelho por milhão de habitantes[38]). Além da escassez numérica, nota-se uma distribuição assimétrica dos recursos. Por exemplo, do total de aparelhos em funcionamento, metade encontra-se na região sudeste, enquanto a região norte conta com apenas 5% deste total. Cinco Estados brasileiros não têm aparelhos de PET, a maioria na região amazônica. Essa distribuição de equipamentos é inversamente proporcional à incidência e mortalidade por câncer de colo de útero, que são maiores nos locais com Índices de Desenvolvimento Humano menor. Considerando-se que o câncer de colo uterino tem estreita relação com o desenvolvimento sócio-econômico, a disponibilidade e os custos dos exames são questões imprescindíveis no manejo dessa doença.

Uma solução com melhor relação custo-benefício e com maior distribuição geográfica de maquinário é a RNM: há milhares de aparelhos no Brasil, espalhados em todos os Estados[39]. Esse exame vem sendo investigado nos últimos anos na predição de resposta ao tratamento e no prognóstico em diversos tumores, entre os quais o de colo de útero. Uma das suas grandes vantagens é que o estudo é feito sem a utilização de radiação.

1.6 Ressonância Nuclear Magnética (RNM)

A RNM foi inventada por Paul C. Lauterbur, em setembro de 1971, sendo a publicação com a teoria envolvida realizada dois anos após[39,40]. Por definição, RNM é uma técnica de exame de imagem em radiologia utilizada para estudos anatômicos e funcionais do indivíduo. Para fazer um estudo de RNM, o paciente é posicionado num scanner, que forma um forte campo magnético ao redor da área a ser estudada. Os prótons (íons de hidrogênio) localizados nos tecidos que contém água são usados para criar um sinal que é processado para formar imagens do corpo.

O átomo é constituído por uma parte central (núcleo) ao redor da qual orbitam os elétrons. O núcleo, apesar de infinitamente menor que a eletrosfera (onde os elétrons orbitam), contém quase toda a massa do átomo. Essa massa advém de estruturas chamadas núcleons, que são subdivididas em prótons e nêutrons. Em se tratando de elétrons, normalmente o seu número é semelhante ao número de prótons (número atômico), para que assim haja estabilidade elétrica, uma vez que elétrons tem carga negativa e prótons tem cargas positivas. De um modo geral, há 3 tipos de movimento num átomo: 1) os elétrons giram ao redor do próprio eixo; 2) os elétrons giram ao redor do núcleo; 3) o núcleo gira em torno do próprio eixo. Os princípios da RNM dependem das características do movimento ao redor do próprio eixo nos diferentes tecidos, movimento este denominado *spin*. Núcleos com número semelhante de prótons e nêutrons têm metade dos *spins* em um sentido (por exemplo, horário) e metade em outro (por exemplo, anti-horário). Entretanto, quando o número de prótons difere do número de nêutrons, os *spins* dessas partículas não são diametralmente opostos, o que gera um momento angular no núcleo conhecido como núcleo ativo de RM[41].

Núcleos ativos de RM tem uma característica em comum que é a tendência a alinhar seu eixo de rotação com a exposição a um determinado campo magnético. A soma destes

spins alinhados resulta num vetor (momento magnético), cuja força é específica de cada núcleo e determina a sensibilidade à RNM. No caso deste exame, utiliza-se o núcleo do hidrogênio como o núcleo ativo de RM pela sua abundância nos tecidos humanos.

Na ausência de exposição a um campo magnético, os momentos magnéticos do núcleo de hidrogênio estão randomicamente orientados. Entretanto, após exposição a um campo magnético, ocorre um alinhamento deles: uma parte na mesma direção (sentido paralelo) e uma parte menor para o sentido anti-paralelo[41].

Em termos práticos, a energia do campo magnético oscilatório é temporariamente transferida ao paciente na frequência de ressonância adequada. Os átomos de hidrogênio excitados emitem um sinal de radiofrequência que é mensurado por uma bobina receptora. Esse sinal pode ser então utilizado para codificar a posição através de variações no campo magnético principal utilizando bobinas com diferentes gradientes. O contraste entre diferentes tecidos é determinado pela velocidade à qual os átomos excitados regressam ao estado de equilíbrio[42].

A RNM requer um campo magnético capaz de ser ao mesmo tempo forte e uniforme. Essa "força" é medida em tesla (T) – embora a maioria dos sistemas opere com 1,5T, há comercialmente disponíveis sistemas de 0,2 até 7T[43].

O contrastamento da imagem pode ser modificado através das diversas ponderações do exame: cada tecido retorna ao seu estado de equilíbrio após uma excitação independente processada em T1 (*spin-lattice*) e T2 (*spin-spin*).

Para se criar uma imagem ponderada em T1, mais magnetização é recuperada antes de se mensurar o sinal através da mudança do tempo de repetição. Essa imagem é útil para acessar a gordura dos tecidos, caracterizar lesões hepáticas e para imagens pós-contraste. No caso de imagem ponderada em T2, mais magnetização é perdida antes de se mensurar o sinal através da mudança do tempo de eco (*echo time*). Tal processamento é útil para detectar edema, revelar lesões na substância branca e acessar a anatomia da próstata e útero[17].

1.7 Sequência de Difusão e Seu Papel no Câncer Cervical

Uma das questões essenciais no estudo e manejo dos tumores é a habilidade de mensurar a resposta ao tratamento. Isso permite otimizar a terapia, alterar estratégias para

diminuir toxicidades ou mesmo evitar esforços desnecessários. Persistir na estratégia inadequada resulta no crescimento acelerado do tumor, desenvolvimento de mecanismos de resistência tumoral ao tratamento, ao mesmo tempo em que se incrementa o dispêndio desnecessário[1]. A maioria das estratégias atuais de acesso à resposta recai nas alterações anatômicas e morfológicas que, sabidamente, ocorrem após mudanças biomoleculares nos grupos de respondedores[44-46]. Devido a grande heterogeneidade tumoral, é improvável que todos os cânceres de um determinado tipo histológico responderão a uma terapia específica[47,48], o que reforça a necessidade de se buscar um marcador precoce e eficaz que possa identificar subgrupos que eventualmente necessitem de terapia personalizada.

A RNM é capaz de aferir a difusão das moléculas de água através dos tecidos. Num meio isotrópico, as moléculas de água naturalmente se movem de maneira randômica – o chamado movimento Browniano - e isso se relaciona com a energia termocinética. Nos tecidos biológicos, contudo, a difusão pode ser anisotrópica. Por exemplo, uma molécula de água dentro do axônio tem baixa probabilidade de cruzar a barreira da mielina. Assim, essa molécula se move preferencialmente no sentido da fibra. Entretanto, essa movimentação aleatória é impedida pela interacão com os compartimentos celulares, incluindo a membrana e as organelas celulares. A restrição à difusão é diretamente proporcional ao grau de celularidade de um determinado tecido. A restrição acentuada é especialmente observada em tumores primários ou metastáticos em virtude do número aumentado de células com membranas intactas em relação aos tecidos sadios adjacentes. Em contraste, num microambiente com menor densidade celular e com membranas não intactas (por exemplo, um centro necrótico de uma grande massa tumoral), as moléculas de água são capazes de se movimentar mais livremente, ou seja, têm menor restrição. Desta forma, a RNMd (Ressonância Nuclear Magnética – sequência de difusão) é sensível ao movimento microscópico das moléculas de água e permite uma caracterização não-invasiva dos tecidos baseada nas diferenças dessas propriedades de difusão[49-51].

A literatura mais recente tem sugerido que a RNMd pode ser utilizada como um marcador indireto da celularidade tumoral, observando a mobilidade das moléculas de água nos tumores[51-56], apesar da dificuldade de interpretação dos dados oriunda da heterogeneidade biológica na prática clínica[57].

Após, e mesmo durante a terapia anticâncer bem sucedida, alterações na densidade celular devidas a necrose e apoptose causam mudanças significativas na difusão da água, o que pode ser detectado pela RNMd. Além disso, essas mudanças acontecem precocemente aos indicadores macroscópicos indicadores de resposta, como tamanho e volume tumoral[46,58].

O Coeficiente de Difusão Aparente (CDA) é uma variável quantitativa derivada da RNMd e que corresponde à magnitude da difusão de água. Ele tem sido amplamente utilizado como um marcador para a resposta terapêutica em vários tipos de tumor, incluindo os do cérebro, de células renais, da mama, do fígado, musculoesqueléticos, de cabeça e pescoço, de próstata e útero[17].

À semelhança de estudos envolvendo 18-FDG PET, a RNMd demonstrou alta sensibilidade e especificidade na identificação de tumores cervicais e linfonodos positivos[17]. Além disso, dados recentes sugerem que alterações nos valores de CDA durante a radio-quimioterapia também podem ser fatores preditivos de resposta e fatores prognósticos. Uma vez iniciada a terapia, há edema celular, necrose e morte celular programada. Nessa sequência, há perda da homeostase hídrica celular e ajustes com a água extracelular podem se refletir em mudanças no CDA. O CDA pode diminuir rapidamente e permanecer assim por várias horas – efeito do edema inicial. Isso é seguido por um aumento progressivo durante dias devido à morte celular. Valores de CDA elevados estão correlacionados histologicamente a áreas de necrose tumoral e redução da densidade celular[59,68-75].

Vários estudos têm mostrado correlação negativa entre o CDA e a densidade das células tumorais, em parte devido à dificuldade de difusão da água frente às barreiras impostas por adensamentos celulares tumorais. Durante um tratamento eficaz, em que as células tumorais são continuamente destruídas, o CDA tem tendência a aumentar devido à redução nessas barreiras. Além disso, características específicas da RNMd, como a capacidade de mapear as alterações celulares sem o uso de contraste e sua curta demanda de tempo para varredura, a tornam um método atraente para avaliar a resposta ao tratamento.

Há poucos relatos do uso da RNMd em órgão fora do crânio porque são frequentes os artefatos de movimentação durante o exame. Entretanto, com o desenvolvimento

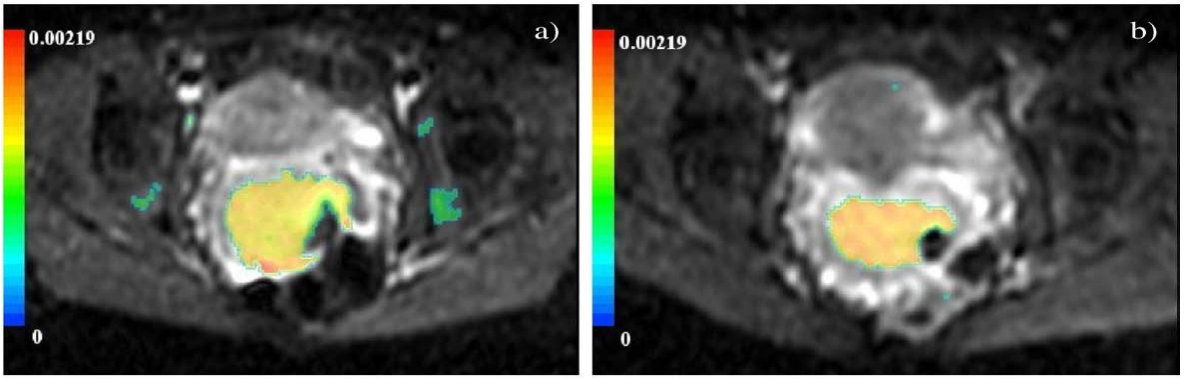
tecnológico, várias estratégias têm sido utilizadas para reduzir esse entrave, permitindo avaliar melhor a resposta ao tratamento[60-62].

Num estudo com 14 pacientes com câncer avançado de reto, Dzik-Jurasz et al. verificaram que a avaliação do CDA realizado antes do tratamento teve uma correlação inversa com a porcentagem de resposta tumoral após RT/QT[63].

Nos tumores de colo uterino, a RNMd foi investigada como ferramenta de auxílio na diferenciação entre o cérvix normal e o patológico[64], além de monitorar a resposta ao tratamento apos a RT[65,66].

Liu et al.[67] avaliaram as mudanças em valores de CDA em tumores de cabeça e pescoço submetidos a radio-quimioterapia e encontraram um número significativamente maior do CDA após a terapia bem sucedida. Este estudo também demonstrou vários limiares de CDA para prever a taxa de resposta completa a radio-quimioterapia, com uma sensibilidade e especificidade de 70% e 81,8%, respectivamente.

Em outro estudo, Harry et al.[1] mediram o CDA no início, no meio, e no final do tratamento de 20 mulheres com câncer do colo do útero localmente avançado e encontraram correlação significativamente positiva entre o aumento do CDA durante o tratamento e maiores taxas de resposta clínica e radiológica (Figura 6).



Fonte: Harry et al[1].

Figura 6 - Exemplo de uma paciente com câncer cervical tratada com radio-quimioterapia radical primária, mostrando redução da área em que há restrição à difusão da água. (a) À esquerda, antes do tratamento; (b) à direita, durante o tratamento.

Estes dados preliminares sugerem que alterações precoces nos valores de CDA poderiam ser um biomarcador da resposta terapêutica durante a radio-quimioterapia e, assim, justificar uma investigação mais aprofundada.

Essa capacidade de o CDA conseguir quantificar pequenas mudanças na arquitetura celular num estágio tão precoce do tratamento pode ser utilizada para aperfeiçoar o tratamento nas pacientes com câncer de colo uterino. Pode-se inferir que, sendo o CDA uma medida semi-quantitativa indireta da funcionalidade tumoral, ele poderia guardar em si informações comportamentais dos tumores em termos de desfechos clínicos antes mesmo de se iniciar o tratamento. Pelo menos em teoria, seria possível modular a intensidade e agressividade do tratamento, dependendo das características funcionais encontradas nos exames de estadiamento.

A tabela 1 traz um resumo esquemático dos estudos publicados que avaliaram o uso de RNMd no câncer do colo do útero.

Tabela 1: Resumo dos principais estudos da literatura. (continua na próxima página...)

Autor	N	Histologia	EC	Tesla	FOV	b-valor	TR (ms)	Espessura de corte	Momento de aferição
Vanessa Harry[1]	20	18 CEC 2 Adeno	IB2-IVA	1,5	40x40	1000	4000	6mm	0, 14d, fim tratamento
Vaida Atstupenaite[68]	65	56 CEC, 6 adeno 3 outros	IB-IVB	1,5	-	50, 400, 800	-	-	0, 6m pós-tratamento
Patrick Z. McVeigh[14]	47	37 CEC 5 Adeno 5Adenoesc	IB-IVA	1,5	32x32	600	4000	9mm	0, 3-6 meses do fim tto
A Le Roux[69]	17	-	IIB-IVB	1,5	32x32	500, 1000	5200	6mm	0, 14d, última semana
Y. Liu[90]	17	17 CEC	IB-IVB	1,5	36x36	0, 1000	4000	6mm	0, 15d (subgrupo de 8 pctes), 1m e 2m pós-tto
Supriya Chopra[98]	20	-	NA	3	40x40	0, 500	6000	3mm	0, 1sem apos fim tto
Rizzo[70]	17	14 CEC 3 adeno	IB1-IVA	1,5	34x34	0, 50, 250, 500, 900	6000	5mm	0, fim
Antonin Levy[71]	49	42 CEC 6 adeno 1 neuro-endocrino	IB1-IVA	1,5	36x36	0, 600, 1000	-	6mm	0, 2m apos fim
Hyun Su Kim[72]	24	21 CEC 3 adeno	IB1-IV	3T	35x35	0, 1000	8000	5mm	0, 4sem, 1m apos fim

Tabela 1 (continuação): Resumo dos principais estudos da literatura.

Autor	Matriz	ROI	Dose RT	Dose Braqui	QT	QT associada	Tempo aquisição
Vanessa Harry[1]	128x96	manual	40Gy/25	Césio 22,5Gy Pto A	CDDP 40	sempre	01:04
Vaida Atstupenaite[68]	-	manual	-	-	-	sempre	-
Patrick Z. McVeigh[14]	128x128	manual	-	-	-	Nem sempre	04:00
A Le Roux[69]	128x128	manual	-	-	-	sempre	5:00
Y. Liu[90]	128x128	manual	42Gy no Pto B	60Gy/ 12fr	CDDP 40	sempre	1:04
Supriya Chopra[98]	128x128	manual	50 Gy/25 Fr	20Gy/5Fr	CDDP 40	Sempre	-
Rizzo[70]	-	manual em 1 corte copiado p/outros cortes	-	-	-	RT QT RT/QT	-
Antonin Levy[71]	128x128	manual	45Gy	15Gy LDR	CDDP 40	RT +/- QT	1:04
Hyun Su Kim[72]	128x108	manual	50,4 Gy	24Gy/6Fr	CDDP 30 1x/sem CDDP 60 + 5FU 1000 3/3sem	Sempre	2:15

2. RELEVÂNCIA CLÍNICA E JUSTIFICATIVA

Mulheres com câncer de colo uterino localmente avançado ainda têm um risco de 20-40% de apresentar persistência de doença ou recidiva após a radio-quimioterapia definitiva. Existe uma necessidade clínica não atendida de estratificar as pacientes em risco maior ou menor de resposta oncológica ao tratamento e outros desfechos clínicos, o que poderia determinar uma terapia mais direcionada e inclusive aumentar as chances de cura. Exames como o PET são utilizados com essa finalidade, porém o dispêndio e o número reduzido de centros nos países em desenvolvimento constituem barreiras quase intransponíveis para os principais locais de grande incidência do câncer colo uterino, daí a necessidade de se buscar alternativas como a RNMd.

As avaliações de imagens de RNMd podem ser feitas de diversas maneiras. No entanto, nem o tempo ou o modo de análise dessas imagens foi definido no câncer cervical. A conclusão bem sucedida deste projeto permitirá que os médicos consigam mais parâmetros para interpretar a RNMd e integrá-la ao arsenal diagnóstico, possibilitando estratificar pacientes com câncer cervical tratados com radio-quimioterapia definitiva e adotar uma abordagem mais específica.

Baseado na hipótese de que a difusão e suas derivadas quantitativas aferidas antes do início do tratamento poderiam ser utilizadas como biomarcadores prognósticos, este estudo pretende verificar se as diferentes medidas de CDA podem realizar esta tarefa. Os resultados poderão trazer contribuição significativa na estratégica de tratamento do câncer do colo do útero.

3. OBJETIVOS

1. Avaliar a associação entre os valores de CDA (mínimo, médio, máximo e do desvio padrão) avaliados antes do tratamento com variáveis de estadiamento (Estadiamento FIGO, Presença de Linfonodo Patológico, Invasão de Paramétrios, de Vagina, de Reto ou Bexiga, de Cavidade Endometrial, de Miométrio e Volume Tumoral);

2. Verificar se os valores de CDA (mínimo, médio, máximo e do desvio padrão) são fatores prognósticos.

4. ARTIGO

BMC Cancer, Impact Factor 2015: 3.26

ABSTRACT

Purpose:

To investigate the association of pre-treatment Diffusion Weighted (DW) Magnetic Resonance Imaging (MRI) parameters with baseline clinical features and clinical outcomes (local regional control (LRC), disease free survival (DFS) and disease specific survival (DSS)) in cervical cancer patients treated with definitive chemoradiation.

Methods and Materials:

This was a retrospective study approved by an institutional review board that included 66 women with cervical cancer treated with definitive chemoradiation who underwent pre-treatment MRI at our institution between 2012-2013. A region of interest (ROI) was manually drawn by one of three radiologists with experience in pelvic imaging on a single axial CT slice encompassing the widest diameter of the cervical tumor while excluding areas of necrosis. The following apparent diffusion coefficient (ADC) values ($x10^{-3}$ mm^2/s) were extracted for each ROI: Minimum - ADCmin, Maximum - ADCmax, Mean - ADCmean, and Standard Deviation of the ADC - ADCdev. Receiver operating characteristic (ROC) curves were built to choose the most accurate cut off value for each ADC value. Correlation between imaging metrics and baseline clinical features were evaluated using the Mann Whitney test. Confirmatory multi-variate Cox modeling was used to test associations with LRC (adjusted by gross tumor volume – GTV), DFS and DSS (both adjusted by FIGO stage). Kaplan Meyer curves were built for DFS and DSS. A p-value < 0.05 was considered significant. Women median age was 52 years (range 23-90). 67% had FIGO stage I-II disease while 33% had FIGO stage III-IV disease. 82% had squamous cell cancer. 88% received

concurrent cisplatin chemotherapy with radiation. Median EQD2 of external beam and brachytherapy was 82.2 Gy (range 74-84).

Results:

Women with disease staged III-IV (FIGO) had significantly higher mean ADCmax values compared with those with stage I-II (1.806 (0.4) vs 1.485 (0.4), p=0.01). Patients with imaging defined positive nodes also had significantly higher mean (±SD) ADCmax values compared with lymph node negative patients (1.995 (0.3) vs 1.551 (0.5), p=0.03). With a median follow-up of 32 months (range 5-43) 11 patients (17%) have developed recurrent disease and 8 (12%) have died because of cervical cancer. ROC curves based on DSS showed optimal cutoffs for ADCmin (0.488 x 10^{-3}), ADCmean (0.827 x 10^{-3}), ADCmax (1.838 x 10^{-3}) and ADCdev (0.148 x 10^{-3}). ADCmin higher than the cutoff was significantly associated with worse DFS (HR = 3.632 – 95% CI: 1.094-12.054; p = 0.035) and DSS (HR = 4.401 – 95% CI: 1.048-18.483; p = 0.043).

Conclusion:

Pre-treatment ADCmax measured in the primary tumor may be associated with FIGO stage and lymph node status. Pre-treatment ADCmin may be a prognostic factor associated with disease-free survival and disease-specific survival in cervical cancer patients treated with definitive chemoradiation. Prospective validation of these findings is currently ongoing.

BACKGROUND

In Brazil, it is estimated that 18,500 women are diagnosed with cervical cancer annually, and 8,400 die[1]. While screening rates for cervical cancer have improved in many countries, there are still a significant number of women who present with locally advanced disease that will require definitive treatment with chemoradiation. Advances in image-guided brachytherapy using Magnetic Resonance Imaging/planning (MRI) rather than 2-dimmensional techniques is significantly improving the outcomes, and changing their patterns of recurrence[2]. With image-based brachytherapy the vast majority of these patients are achieving local control of their tumors with limited serious acute or late morbidity. More women are now recurring with distant rather than local failures with marginal outcomes with systemic therapy in these cases[3]. Efforts are now underway on the OUTBACK trial[4], for example, to potentially improve these clinical outcomes with the addition of systemic chemotherapy following the completion of definitive chemoradiation. One of the challenges of this approach is being able to identify patients at highest risk for poor outcomes following chemoradiation alone. Advances in functional imaging with Positron Emission Tomography (PET) and quantification of a standardized uptake value (SUV) can provide prognostic information that may be helpful in identifying women populations at higher risk of failure, thereby allowing for an enriched patient population that is more likely to benefit from escalated therapy[5-7.]

In low-middle income countries there are a limited number of cyclotrons available for PET imaging making it impossible to integrate this technology into the routine management of cervical cancer patients. MRI is, however, readily available and routinely utilized for cervical cancer staging in many countries but standard imaging sequences only provide anatomical, and not functional, information. Newer MRI sequences such as diffusion-weighted imaging (DWI) provide functional information by characterizing the diffusion of water between cells[8-10]. This can be quantidated, similar to an SUV on PET scans, by calculating an apparent diffusion coefficient (ADC) value. Previous investigators have demonstrated high concordance of tumor sub volumes with increased metabolic activity on PET with increased cellular density on DWI imaging suggesting ADC values may have similar prognostic value as SUVmax[8,11].

DWI imaging has previously been studied in cervical cancer patients with mixed results regarding its utilization as a prognostic/predictive marker[14-16,19-22]. Given the variation in correlations with DWI imaging, we investigated whether baseline MRI DWI imaging features correlate with clinical outcomes in women with locally advanced cervical cancer treated with definitive chemoradiation.

MATERIAL AND METHODS

This was a retrospective study of cervical cancer women treated at Barretos Cancer Hospital, approved by the Research Ethics Committee. Patients were treated using radiation therapy with or without concurrent chemotherapy and who had an MRI of the pelvis performed prior to the start of treatment between January 2012 and March of 2013. A total of 135 patients were identified. 46 were excluded from further analysis because either their MRI was not performed at our institution or diffusion weighted imaging was not performed. 10 additional women were excluded because they were treated with palliative intent and 13 more were excluded because they did not have sufficient clinical follow-up information available. This left 66 women available for complete analysis.

The study group was classified according to the revised 2009 FIGO staging system. The extent of tumor involvement was based on both clinical examination and MRI findings (i.e. a patient with parametrial involvement on clinical examination but clear involvement on MRI imaging to the pelvic sidewall was classified as FIGO Stage IIIB). Positive lymph nodes were based on MRI findings. A lymph node was considered positive if it had a maximum diameter larger than 1 cm with heterogeneity of signal or an irregular contour. Enlarged lymph nodes were not routinely pathologically confirmed.

Eight patients received radiation alone and 58 were treated with chemoradiation. All 66 women received high dose rate (HDR) brachytherapy as a component of their treatment. The mean (SD) external beam and HDR doses were: 44.92 (0.62) Gy and 27.05 (1.67) Gy (7 Gy x 4 being the most common fractionation), respectively. The mean (SD) equivalent dose in 2-Gy fractions (EQD2) for external beam plus HDR-brachytherapy was 82.2 (2.8) Gy. There was no lymph node boost.

Radiation was delivered using a standard linear accelerator with either 6MV or 15MV beams and planned using a 3D planning method with organ at risk and target volumes contoured by a radiation oncologist. Intensity modulated radiation therapy was not used. All patients were planned using Eclipse version 8.6 (Varian Medical Systems, Palo Alto, CA, USA).

For the brachytherapy, four fractions of HDR using a tandem and ovoid applicator were delivered to all patients (except two that only received three fractions of 7 Gy). The dose was prescribed to point A and was planned based on 2-dimmensional films. Bladder and rectal points were placed as per ICRU 38 guidelines. The constraints for a prescription of 7 Gy were 71% (bladder) and 58% (rectum). Dose prescription was diminished to 6.5 Gy or 6 Gy when the constraints were extrapolated. Brachytherapy planning was performed using GammaMedTM (Varian Medical Systems Inc., Palo Alto, CA, USA). All brachytherapy insertions were guided by ultrasound.

The majority of women (82%) were treated with concurrent cisplatin chemotherapy at a dose of 40 mg/m^2 weekly. Four women received concurrent carboplatin and eight did not receive concurrent chemotherapy.

All patients were followed up with physical exam, abdominal/pelvic imaging and surveillance pap smears every three to six months.

Disease recurrence was determined radiographically by RECIST 1.1 criteria[12] and was not pathologically confirmed. Local regional control was defined as the time from biopsy to local (uterine cervix or vagina) or regional recurrence (pelvic lymph node). Disease free survival (DFS) was defined as the time from biopsy to tumor progression. Disease specific survival (DSS) was defined as the time between biopsy to death by cancer.

Imaging Technique and Analysis

All images were performed at baseline assessment (before any treatment) on one of two scanners: Achieva 3.0 Tesla, Philips Healthcare, Netherlands or a Signa HDX'T 1.5 Tesla, GE Healthcare, Milwaukee. All patients had trans-vaginal ultrasound gel administered prior to the start of their MRI. The sequences acquired included T2-weighted sequences of the whole pelvis and abdominal region below the renal arteries, axial T1-weighted sequences of

the whole pelvis, T2-weighted sequences in the sagittal, axial and coronal planes at an angle through the plane of the cervix, and diffusion-weighted sequences. For the diffusion sequence, the field of view was 40x40, the matrix size was 512, with b-values of 0, 600 (3T scanner) and 0, 800 (1.5T scanner). Acquisition time was 6 min. Voxel size was 2.34 mm (RL), 3.19 mm (AP). Repetition time was 1800 ms and slice thickness was 3 mm.

After generating the ADC maps, a region of interest (ROI) was manually drawn by one of three experienced radiologists (F.R.L., A.K.B.J.N., R.R.R.) on a single DWI slice that showed the lesion at its maximum diameter, using axial FSE T2WI for guidance. PACS software (PixViewer, Viewer MPR - PIXEON) then calculated the ADC minimum (ADCmin), mean (ADCmean), maximum (ADCmax) and standard deviation of the ADC values (ADCdev) ($x10^{-3}$ mm^2/s) of the chosen region (Figure 1).

Statistical Considerations

The Mann Whitney test was used to compare ADC values of clinical-pathological and treatment-related factors including: FIGO stage (I/II vs III/IV), histology (squamous vs non-squamous), tumor grade (1-2 vs 3), lymph node status (N+ vs N-), parametrial invasion (yes vs no), vaginal invasion (yes vs no), rectal/bladder invasion (yes vs no), Gross Tumor Volume (GTV) (greater than or less than the median), radiation dose to the primary tumor expressed as an EQD2 (greater than or less than the median) and usage of chemotherapy (yes vs no). ROC curves were built in order to choose a cutoff value for ADC variables. Confirmatory multivariate Cox model analysis was used to test ADC values and associations with DFS and DSS. These models were adjusted by FIGO stage. LRC was evaluated by confirmatory logistic regression using the GTV as the adjustable variable. Three-year survival rates (DFS and DSS) were estimated according to Kaplan Meyer method. Significance level was set at 5% for all statistics.

Availability of Data

The data that support our findings will not be shared due to patient privacy issues and the lack of written consent form signed by patients (retrospective study).

RESULTS

Correlations between imaging parameters and baseline clinical features

Of the 66 women included in the analysis, 44 had FIGO stage I-II disease while 22 had stage III-IV disease. Seventy-one percent had well or moderately differentiated disease and 82% had squamous cell cancer. Additional patient details are presented in Table 1.
Table 2 shows comparisons between baseline clinical features and different ADC values. Women with FIGO stage III-IV disease had significantly higher mean ADCmax values compared with stage I-II (1.8 vs. 1.5, p=0.007). Patients with imaging defined positive nodes also had significantly higher mean ADCmax values compared with lymph node negative ones (2.0 vs. 1.6, p=0.029). No other significant correlations were seen.

Treatment Outcomes

After a median follow up of 32 months (range 5-43), 11 patients (17%) developed recurrent disease (from whom 3 were still alive by the time of the analysis) with a median time to recurrence of 9 months (range 5-39). Two patients developed pelvic recurrence only (one an in-field recurrence in the cervix and one in a left external iliac lymph node), five developed distant metastasis only, and four developed both pelvic/distant disease recurrence. For these four patients, the pelvic component of failure included: two in the cervix only and two in the cervix and pelvic lymph nodes. Six out of 8 women did not receive concurrent chemo (and were free of disease by the time of the analysis.

There have been a total of nine deaths in the 66 women with a median time to death of 13 months (range 9-32). Eight patients (12% of the total 66) have died from cervical cancer (they presented cancer recurrence) and one patient died from a pulmonary embolus who had no evidence of disease at the time of death. Baseline clinical features of the eight patients who died from cervical cancer include: median age 57 (range 36-74), 6/8 SCC, 8/8 moderate/poorly differentiated, 6/8 FIGO stage III-IV, 6/8 received chemotherapy, median GTV volume 154 cc, and median EQD2 of external beam and brachytherapy was 82 Gy (range 74-83.9).

The three-year LRC and DFS for the entire group were 89.3% and 84.8%, respectively. The three-year DSS was 87.5%. Table 3 shows the univariate analysis for correlation between clinical characteristics with DFS and DSS.

Cutoff points for predicting the analyzed outcomes were chosen by ROC curve analysis for ADCmin (0.488 x 10^{-3} mm^2/s, AUC = 0.57; 95% CI: 0.33-0.79), ADCmean (0.827 x 10^{-3} mm^2/s, AUC = 0.72; 95% CI: 0.56-0.88), ADCmax (1.838 x 10^{-3} mm^2/s, AUC = 0.70; 95% CI: 0.50-0.90) and ADCdev (0.148 x 10^{-3} mm^2/s, AUC = 0.60; 95% CI: 0.41-0.78).

Tables 4 and 5 show the multivariate analysis for LRC and survival, respectively. No ADC value was correlated with LRC. ADCmin higher than the cut off was independently associated with worse DFS (HR = 3.6 – 95% CI: 1.09-12.05; p = 0.035) and DSS (HR = 4.4 – 95% CI: 1.05-18.5; p = 0.043). Figures 2 and 3 show Kaplan Meyer curves for DFS and DSS, respectively.

DISCUSSION

Recent advances in imaging have improved the ability to characterize the full extent of local disease extension, pelvic/para aortic lymph node involvement, and the presence of distant metastasis in cervical cancer patients. Functional information derived from PET/CT like the SUVmax can also be prognostic[5-7]. Unfortunately this advance in PET/CT imaging is not readily available in developing countries such as Brazil. MRI imaging is, however, more accessible. MRI has the advantage of providing superior soft tissue anatomy compared with CT, which in turn improves assessment of locoregional disease. In addition, functional MRI sequences have the potential to make MRI more than just an anatomic tool. Areas of interest can be contoured on DWI imagined and be quantified by calculating an ADC value. DWI imaging is also very practical in that it does not require much additional scan time or require intravenous contrast[10,14-16].

In this study we found that pre-treatment ADCmax was significantly correlated with FIGO stage and radiographically enlarged lymph nodes. A recent study from Memorial Sloan Kettering Cancer Center also showed a significant correlation between pretreatment ADCmean with FIGO stage and the presence of positive lymph nodes[19]. However, while their study showed significantly higher ADCmean for earlier staged disease and uninvolved nodes

we found exactly the opposite result (higher values of ADCmax for higher staged disease and positive nodes). This difference demonstrates some of the challenges of comparing results between studies given non-standardized methods for calculating and reporting ADC results and is discussed further below.

Investigating whether baseline ADC values might be a prognostic imaging biomarker may be more important than a correlation with baseline tumor characteristics. If validated this would give us an opportunity to consider risk adapting patients at the start of their treatment rather than waiting until a recurrence or subjecting all patients to an increased intensity regimen, where only a few might actually benefit. Whether ADC values are prognostic, similar to SUVmax, is an area of active investigation with existing publications showing both increased and decreased pre-treatment ADC tumor values correlating with clinical outcomes[13-18].

The literature to date using ADC for assessing prognosis has predominantly focused on metrics such as ADCmin, ADCmax, ADCmean, and ADC percentiles when a histogram-based analysis is used. One recent histogram based analysis includes a recent study of 85 cervical cancer women treated with chemoradiation demonstrating a lower baseline absolute and normalized ADC 95th percentile is associated with shorter disease free survival on multivariate analysis[20]. Other groups have reported on using ADC information gleaned from a single MRI slice. In one retrospective study of 45 cervical cancer women treated with a mix of definitive surgery and chemoradiation, a lower pretreatment ADCmean was predictive of both disease free and overall survival[19]. While these are two of the larger studies published to date looking at correlations between ADC values and clinical outcomes in cervical cancer, there are multiple studies that have been published on this topic with variation in the correlation between ADC values and outcomes. Some studies have correlated higher pre-treatment ADC values with inferior outcomes, while others have correlated lower pre-treatment values with inferior outcomes. These inconsistencies are likely related to multiple factors including: the heterogeneity of the patients, different treatments (surgery vs chemoradiation), various histologies (squamous cell cancer vs adenocarcinoma), use of a single slice region of interests for calculating ADC values which can underestimate the true heterogeneity of the overall tumor, different MRI imaging protocols, retrospective study design, different time points for assessing treatment response, and small patient numbers.

These discrepancies point to some of the challenges in comparing data across various studies. Moving forward there needs to be agreed upon imaging and reporting standards so that data can be compared across different institutions. This is not a problem unique to DWI and similar discrepancies have been reported for dynamic contrast enhanced MRI studies in cervical cancer[21].

We looked at standard ADC metrics like the minimum, maximum and mean but also evaluated the ADCdev, which has not been previously reported on. ADCmin and ADCmax represent extreme values that can be very sensitive to tumor composition, i.e., extremely high or extremely low ADC sub-volumes (which could have prognostic value). The fact that ADCmean represents a much larger amount of information (it represents the mean value of all voxels measures including the ADCmin and ADCmax) could explain the observation that it reached significance only in the univariate analysis but didn't do in the multivariate where only ADCmin was significantly associated to outcomes - higher values were correlated with poorer DSS and DFS. A number of studies have linked ADC values to therapy outcomes, with most of them showing that tumors with higher values respond less favorably to therapy[24-28]. Mechanistically this may be explained by the presence of microscopic and macroscopic tumoral necrosis, which can increase ADC values and is linked to poorer outcomes[22,23]. Our data is in contrast however to Nakamura et al[29] who analyzed the combination of ADCmin and SUVmax in 66 women with cervical cancer. Women with lower ADCmin showed decreased OS compared to those with the highest values. The fact that we found exactly the opposite in our study (highest values of ADCmin predicting worse DSS) only exemplifies the difficulties in interpreting this data without standardized reporting.

When looking at the makeup of the patients who died from cervical cancer one can see that although the majority had advanced features (FIGO III/IV disease, moderate/poorly differentiated SCC, and large GTV volumes) that there were many patients with similar features who had positive outcomes. This emphasizes the limitations of our current risk stratification schemes that focus on clinical and pathologic features without integrating information about the biology of the tumors. While the underlying biology responsible for variations in ADC values in cervical cancer is not known it does provide functional information that is currently not incorporated into our standard risk stratification tools. Given that the dominant pattern of failure in our cohort included a component of distant

failure (9 out of 11 cases) it is critical that we identify women at high risk of distant failure as early on in the natural history of their disease as possible in an effort to improve their outcomes. With additional data it's possible that information gleaned from functional imaging could help identify high risk populations either independently or synergistically with our current clinically based stratification.

There are some weaknesses of our study which include its retrospective design. This contributes to differences in the timing and method of assessment of clinical response as well as the different b-values used for the DWI studies. Variation in b-values occurred due to the adoption of different imaging protocols over time. A study published by Hoogendam et al. however reported that changing the tested b-value combinations did not influence the ADC-based differentiation of benign tissue from malignant tissue and so it is not clear if this impacted the results of this study[30]. Also, we limited the number of adjusted variables in the confirmatory multivariate model in order to avoid an over fitting due to the relative small number of events[31]. Hence, we decided to use well-known prognostic factors as adjusted variables such as FIGO stage for DSS and DFS and GTV for LRC. Moreover, patients were treated using 2-dimmentional brachytherapy and did not have their enlarged lymph nodes boosted. This might have impacted the patterns of failure and ultimate treatment outcomes as has been suggested by the improved outcomes using 3-dimmentional image guided brachytherapy data, however, the local failure rates in this series are low and the predominant failure pattern was distant which is in line with more modern image guided outcomes.

These findings need to be validated in a prospective setting and we have already open a clinical trial measuring ADC values at baseline, mid-treatment, and 3 months post-treatment in patients being treated with chemoradiation for cervical cancer. Ultimately a prospective trial will help determine whether baseline or mid-treatment MRI features, as has been suggested by others are independent predictors of outcomes and whether this could be used for selecting patients that may benefit from escalated treatment[32,33].

CONCLUSIONS

Pre-treatment ADCmax measured in the primary tumor may be associated with FIGO stage and lymph node status. Higher pre-treatment ADCmin measured in the primary tumor of cervical cancer might predict worse disease free survival and disease specific survival in patients treated with definitive chemoradiation. Prospective validation of these findings is currently ongoing.

Table 1 - Patient and treatment characteristics.

	n (%)
Number of patients	66
Median age at diagnosis (range)	51.8 (23.3-90.1)
Histology	Squamous: 54 (82%)
	Adenocarcinoma: 7 (11%)
	Adenosquamous: 5 (8%)
Grade (differentiation)	Well: 4 (6%)
	Moderate: 43 (65%)
	Poor: 19 (29%)
FIGO Stage (2009)	IB1-2: 2 (3%)
	IIA1-IIB: 42 (64%)
	IIIA-B: 16 (24%)
	IVA-B: 6 (9%)
Median External beam radiotherapy dose (range)	44.92 Gy (39.6-59.4)
Median HDR Brachytherapy dose (range)	27.05 Gy (21-28)
Median Total external beam and brachytherapy dose as an EQD2 (range)	82.2 Gy (74-83.9)
Concurrent chemotherapy	58 (88%)

Table 2 - Mean ADC values according to tumor stage, lymph node involvement, and MRI assessed disease extent.

	ADC_{min}	ADC_{mean}	ADC_{max}	$ADC_{deviation}$
FIGO Stage	(p=0.077)	(p=0.227)	(p=0.007)	(p=0.070)
I-II (n=44, being 22 with positive nodes)	0.375	0.855	1.485	0.224
III-IV (n=22, being 18 with positive nodes)	0.267	0.901	1.806	0.256
Lymph node	(p=0.902)	(p=0.092)	(p=0.029)	(p=0.154)
Positive (n=40)	0.323	0.959	1.995	0.232
Negative (n=26)	0.341	0.861	1.551	0.197
Parametrial Invasion	(p=0.680)	(p=0.810)	(p=0.081)	(p=0.492)
Present (n=59)	0.332	0.867	1.618	0.223
Absent (n=7)	0.404	0.898	1.371	0.177
Vaginal Invasion	(p=0.190)	(p=0.252)	(p=0.203)	(p=0.887)
Present (n=47)	0.311	0.848	1.624	0.198
Absent (n=19)	0.410	0.925	1.513	0.267
Rectum or bladder Invasion	(p=0.683)	(p=0.184)	(p=0.301)	(p=0.829)
Present (n=21)	0.353	0.904	1.702	0.192
Absent (n=45)	0.339	0.854	1.542	0.231
Gross tumor volume (cc)*	(p=0.172)	(p=0.886)	(p=0.147)	(p=0.468)
> 114.48	0.295	0.862	1.674	0.237
< 114.48	0.383	0.877	1.508	0.206

*Calculated by multiplication of the tumor measures (left-right, anterior-posterior, cranial-caudal)

Table 3 - Univariate analysis for disease specific survival and disease free survival.

			Disease specific survival		Disease free survival	
Variable	**Category**	**n**	**3-y DSS**	**p-value**	**3-y DFS**	**p-value**
FIGO	I / II	44	95.3	0.007	90.9	0.018
	III / IV	22	72		72.7	
Lymph node	Positive	40	79.1	0.015	74.9	0.024
	Negative	26	100		100	
Parametrial Invasion	Present	59	85.9	0.304	83	0.816
	Absent	7	100		100	
Vaginal Invasion	Present	47	84.3	0.265	82.9	0.850
	Absent	19	94.7		89.5	
Adjacent Structures	Present	21	71.1	0.005	69.3	0.015
Invasion	Absent	45	95.3		93	
GTV (*)	<114.48	41	97.6	0.001	95.1	0.003
	>114.48	25	69.4		68	
ADC_{min} (*)	< 0.488	45	93.1	0.060	90.9	0.073
	> 0.488	21	76.2		72.7	
ADC_{mean} (*)	< 0.827	25	100	0.017	96	0.037
	> 0.827	41	79.3		77.9	
ADC_{max} (*)	< 1.838	51	93.9	0.002	90.2	0.053
	> 1.838	15	64.6		66	
ADC_{dev} (*)	< 0.148	16	100	0.088	93.8	0.221
	> 0.148	50	83.2		81.9	

(*) Cutoff values were defined by ROC curve analysis.

Table 4 - Multivariate logistic regression models for local regional control.

Variables	**Category (*1)**	**n**	**HR (*2)**	**95% CI**
ADC_{min}	< 0.488	45	Ref.	
	> 0.488	21	3.9	0.6-27.7 (p = 0.169)
ADC_{mean}	< 0.827	25	Ref.	
	> 0.827	41	1.7	0.2-17.7 (p = 0.650)
ADC_{max}	< 1.838	51	Ref.	
	> 1.838	15	1.3	0.2-10.0 (p = 0.771)
ADC_{dev}	< 0.148	16	Ref.	
	> 0.148	50	0.9	0.1-9.7 (p = 0.934)

HR = Hazard ratio, CI = Confidence Interval, Ref = Reference

(*1) Cutoff values were defined by ROC curve analysis.

(*2) Each model was adjusted by Gross Tumor Volume (GTV: cutoff value = 114.48)

Table 5 - Multivariate models for disease specific survival and disease free survival.

			Disease Specific Survival		Disease Free Survival	
Variable	**Category (*1)**	**N**	**HR (*2)**	**95% CI**	**HR**	**95% CI**
	< 0.488	45	Ref		Ref	
ADC_{min}	> 0.488	21	4.4	1.1-18.5 (p = 0.043)	3.6	1.1-12.1 (p = 0.035)
	< 0.827	25	Ref		Ref	
ADC_{mean}	> 0.827	41	277.3	0.0-2.7 (p = 0.963)	4.9	0.6-39.5 (p = 0.138)
	< 1.838	51	Ref		Ref	
ADC_{max}	> 1.838	15	4.3	1.0 -19.3 (p = 0.056)	2.1	0.6-7.3 (p = 0.255)
	< 0.148	16	Ref		Ref	
ADC_{dev}	> 0.148	50	202.5	0.0-2.4 (p = 0.969)	2.7	0.4-21.1 (p = 0.354)

HR = Hazard Ratio, CI = Confidence Interval, Ref = Reference

(*1) Cutoff values were defined by ROC curve analysis.

(*2) Each model was adjusted by FIGO staging (I/II vs III/IV)

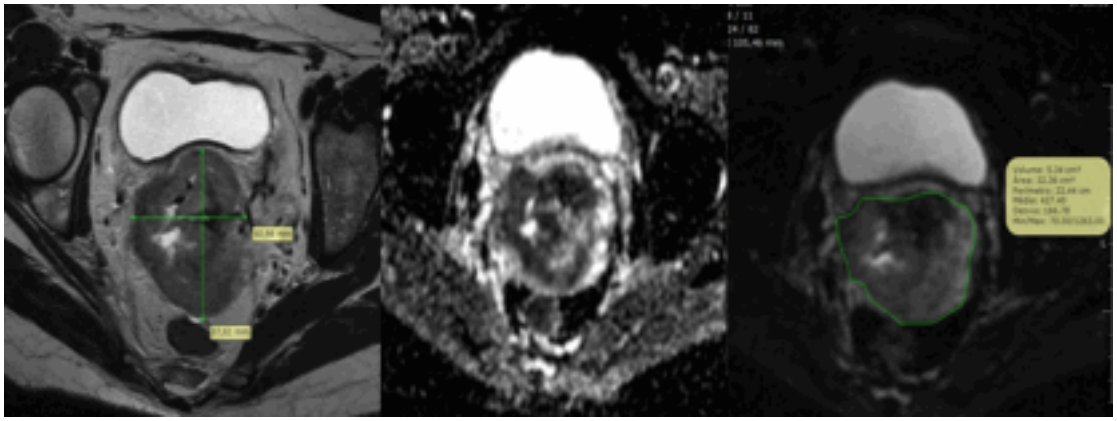


Figure 1: Magnetic resonance imaging examples of axial slices of: T2 weighted (left), diffusion weighted imaging (center), and region of interest drawn on an attenuation diffusion coefficient map (right).

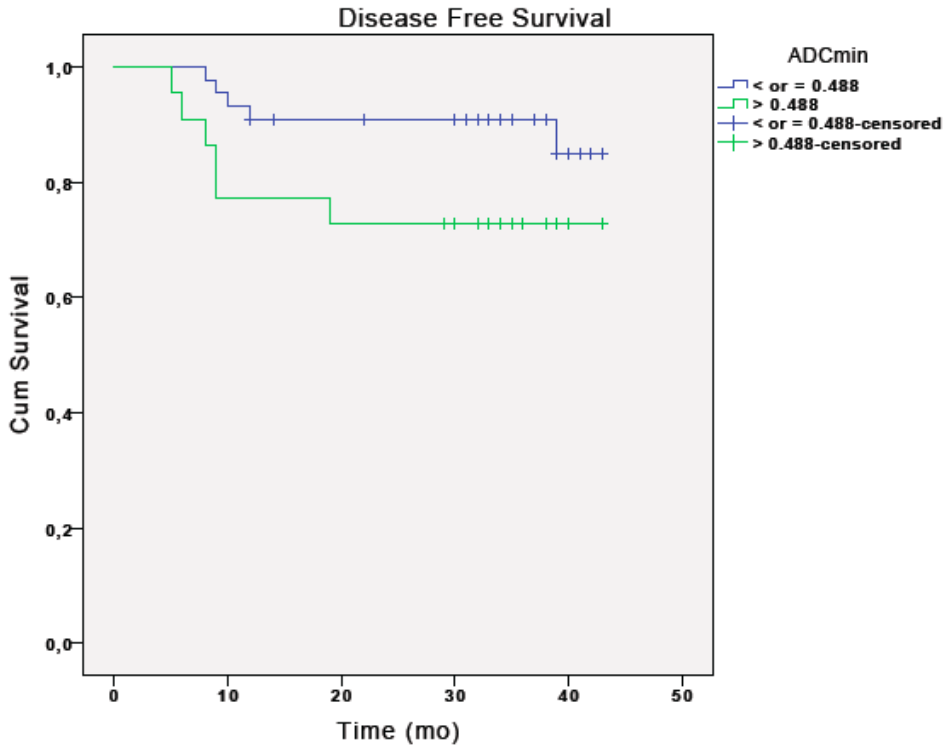


Figure 2: Kaplan Meyer curve for DFS.

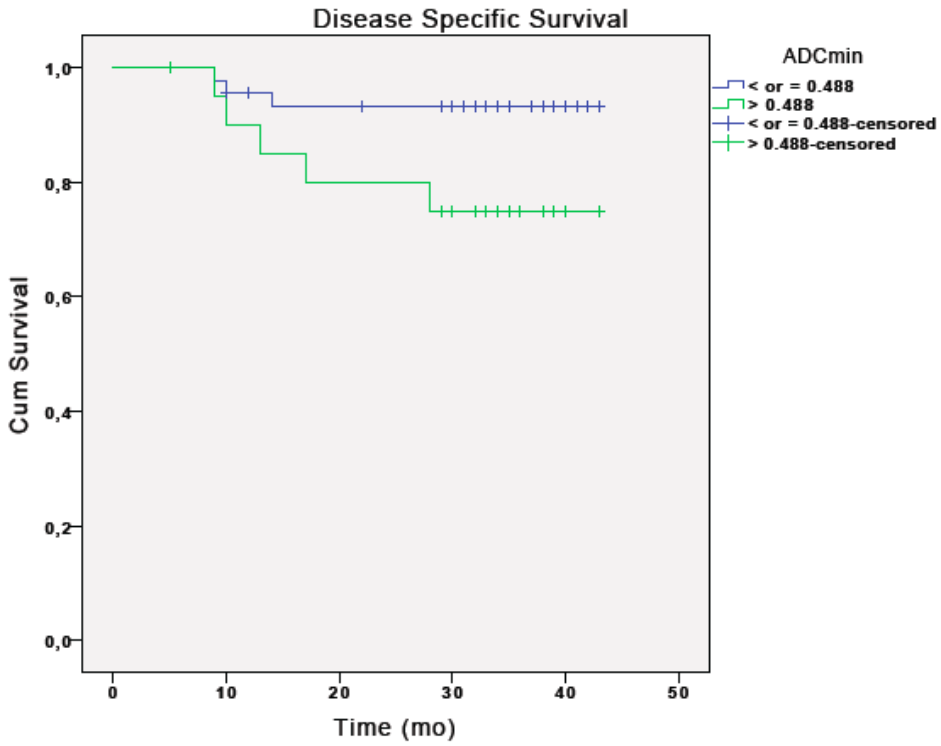


Figure 3: Kaplan Meyer curve for DSS.

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5. DISCUSSÃO

Vários estudos têm sugerido que a RNM, com a sua característica de resolução mais aprimorada para tecidos moles, é o método diagnóstico mais eficaz para a detecção de tumores primários e metastáticos no câncer de colo de útero, constituindo-se na técnica de escolha para a definição da estratégia de tratamento[73,74]. Entretanto, as sequências anatômicas convencionais deste exame são trabalhosas e, por vezes, é impossível realizar o diagnostico diferencial entre doença residual ou fibrose, especialmente nos três primeiros meses após o final do tratamento[75,76], mesmo com a adição de técnica contrastada[77].

Mais recentemente, alguns estudos utilizando a RNM com sequência de difusão sugerem que ela poderia ser sensível a mudanças no microambiente tumoral após a realização do tratamento[78]. O tratamento bem-sucedido resulta em dano significativo para as células tumorais graças a quebra da barreira na membrana, com a subsequente redução do adensamento celular[79].

Há uma explicação teórica que embasa o racional do uso do CDA como biomarcador de resposta ao tratamento: tumores com altos valores de CDA pré-tratamento são mais propensos a serem necróticos[80]. Os tumores necróticos frequentemente são hipóxicos, acidóticos, e mal perfundidos, levando a diminuída sensibilidade à quimioterapia e à radioterapia[80]. Além disso, a distribuição de agentes quimioterápicos em tumores necrosados pode ser menos eficiente devido à vascularização insuficiente[81]. A correlação entre os parâmetros de difusão pré-tratamento e pós-tratamento indica que os tumores com valores de CDA baixos antes do tratamento responderão melhor à quimioradioterapia do que os tumores com altos valores de CDA. A Identificação de pacientes que possam ter uma resposta pobre ao regime de radioquimioterapia ainda antes do tratamento pode permitir, ao menos em teoria, uma alteração precoce no plano terapêutico, como a adição de novos agentes radiossensíveis.

A ressonância magnética é uma técnica de imagem padrão usada na avaliação loco-regional inicial[82,83] do câncer do colo do útero. Enquanto as sequências convencionais fornecem a anatomia dos tecidos moles de modo superior a CT, a adição de sequências funcionais tem o potencial para tornar o exame algo mais do que apenas uma ferramenta anatômica. A adição da sequência de difusão aumenta o tempo de exame de maneira mínima e não requer o uso de contraste. Áreas de interesse podem ser delineadas para o

cálculo do CDA. Postula-se que valores baixos de CDA em tumores possam ser causados pelo aumento da celularidade tecidual ou densidade celular[84-86], porém o quanto isso reflete na taxa de resposta ao tratamento ainda é desconhecido.

O presente estudo verificou que o CDAmáx pré-tratamento foi significativamente correlacionado com o estádio FIGO e *status* linfonodal: mulheres com estádio FIGO III-IV tiveram valores médios de CDAmáx maiores do que as com estádio FIGO I-II, assim como as com linfonodos radiologicamente suspeitos em relação àquelas sem linfonodos suspeitos para acometimento secundário. Nesse contexto, outros grupos também encontraram correlações semelhantes entre valores de CDA inicial e outras características do tumor, incluindo um estudo recente que mostrou associação entre CDAméd com estádio da doença e também com a presença de linfonodos metastáticos[87]. Uma das hipóteses existentes para correlacionar o CDA com desfechos clínicos desfavoráveis é a presença de necrose, que sabidamente se correlaciona com piores desfechos clínicos[88].

Mais importante do que uma associação com as características tumorais é a possibilidade de o CDA ser um biomarcador prognóstico. Caso isso se confirme, haverá a oportunidade de modificar o plano terapêutico antes mesmo do seu início, ao invés de se esperar a evolução clínica pós-tratamento para avaliar a resposta e, só então, discutir outra estratégia terapêutica. Essa mesma estratégia, a título de exemplo, já foi validada com o PET / CT (desfecho substituto): a análise da biologia tumoral mostrou algumas alterações na expressão gênica na via de sinalização PI3K/AKT em pacientes com câncer de colo de útero com resposta metabólica incompleta ao PET que poderiam se correlacionar com piores desfechos clínicos[89].

Alguns estudos têm relatado a associação do CDA com desfechos clínicos de curto prazo, como a resposta precoce ao tratamento irradiante. McVeigh et al.[65] mostraram que, em pacientes com câncer de células escamosas do colo de útero, o percentil 90 do CDA foi significativamente menor nos respondedores do que em não-respondedores. Em outro estudo semelhante, Liu et al.[90] mostraram que os CDAs pré-tratamento de tumores que tiveram uma resposta completa foram também significativamente mais baixos do que os tumores com uma resposta parcial. Por outro lado, a literatura apresenta resultados contraditórios. Alguns pesquisadores demonstraram associação de valores iniciais mais baixos de CDAméd com piores taxas de sobrevida, ao invés de melhor[87]. Duas revisões sistemáticas recentes[91,92] sobre valores de CDA em pacientes com câncer cervical

submetidos à quimioradioterapia definitiva mostraram valores maiores de CDAméd pós-tratamento em comparação com o início do tratamento em pacientes que apresentaram resposta completa. No entanto, dados usando apenas o CDA pré-tratamento para prever resultados clínicos ainda são limitados.

Vários estudos que investigam a capacidade preditiva do CDA inicial relataram resultados heterogêneos. Embora poucos estudos previram maiores chances de resposta completa com menores valores de CDA de base[91,92], outros estudos não confirmaram a existência dessa correlação[1,93]. Embora a maioria dos estudos utilizem metodologia comum de desenhar a região de interesse sobre o tumor enquanto se excluem as regiões de necrose, a heterogeneidade de resultados pode ser explicada porque os valores representam médias do CDA na região de interesse. Desta forma, as regiões focais de restrição maior ou menor à difusão são, muitas vezes, perdidas. Esta poderia ser uma das explicações dos resultados negativos encontrados no presente estudo.

Estas discrepâncias apontam para alguns dos desafios na comparação dos resultados dos diversos estudos: normalmente, eles são compostos de pequenas populações heterogêneas de pacientes, variam no momento em que é avaliada a resposta ao tratamento, incluem diferentes protocolos de imagem, desenham regiões de interesse de forma diferente e analisam diferentes parâmetros relacionados ao CDA. Este não é um problema exclusivo para a RNMd: discrepâncias semelhantes foram relatadas em estudos de perfusão de ressonância magnética no câncer do colo do útero[94]. Desta forma, acreditamos que o presente estudo traz informações valiosas, visto que apresenta uma das maiores cauísticas entre os estudos do gênero, sendo as mulheres tratadas e avaliadas de forma homogênea, na mesma instituição, pela mesma equipe de médicos e pesquisadores.

As limitações do estudo são inerentes ao seu caráter retrospectivo, e podem representar também possíveis explicações para os resultados encontrados: elas incluem as diferenças no momento e método de avaliação da resposta clínica, bem como o uso de diferentes scanners e diferentes valores de b usados entre os aparelhos. Nesse contexto, um estudo publicado por Hoogendam et al.[95] reportou que a alteração das combinações de valor de b para a análise do CDA não influenciam na diferenciação entre lesões benignas e malignas. No presente estudo, 34 pacientes fizeram os exames iniciais em scanner de 3T, e 32 num scanner de 1,5T. No primeiro grupo, os valores de b utilizados foram de 0/800, enquanto no segundo foram 0/600. Outro estudo, entretanto, analisou a reprodutibilidade

da RNMd no parênquima dos rins, fígado e baço de 11 indivíduos hígidos submetidos a exames com os mesmos parâmetros técnicos e analisados por um observador único e concluiu que houve diferenças significativas na mensuração do CDA para os três sítios analisados, da ordem de 7-14%[96]. Assim, não está claro se o fato de a coorte do presente estudo ter usado scanners diferentes e valores de b distintos influenciou nos resultados encontrados, além da própria variabilidade inter-observador.

Em relação à análise dos desfechos clínicos, consideramos que este estudo contribui efetivamente com a literatura existente, sobretudo pelo tamanho da casuística e pelo tempo de seguimento. O valor prognóstico do CDA foi sugerido na literatura por Gbolahan Somoye[97], em estudo publicado após seguimento mediano de 26 meses. O valor mediano do CDA durante o tratamento foi significativamente maior nos sobreviventes em relação aos que morreram (1,55 vs 1,36 x 10^{-3} mm^2/s; p = 0,02). Embora não tenha sido registrada diferença significativa entre o CDA pré e pós tratamento dos sobreviventes em relação aos que morreram, a pesquisa apontou que essa relação possa, talvez, ser evidenciada em outro contexto com maior casuística.

Outro ponto relevante a se mencionar é a limitação do presente estudo em analisar os sub-volumes tumorais. Como afirmado por Chopra et al.[98], a heterogeneidade espacial do tumor na sequência de difusão prediz a resposta parcial à quimioradioterapia em pacientes com recidiva no pós-operatório de câncer cervical. Nesse sentido, a correlação espacial das áreas de resposta com mensurações focais de CDA nos locais correspondentes poderia proporcionar uma melhor compreensão da sensibilidade à radiação de sub-volumes nos tumores heterogêneos e fornecer caminhos para a melhoria adicional da terapêutica.

Devido a todas essas incertezas e heterogeneidades, consideramos que a avaliação do CDA como preditor de resposta e de desfechos clínicos precisa ser validada em um cenário prospectivo. Para isto, iniciou-se no Hospital de Câncer de Barretos um novo estudo, de caráter longitudinal prospectivo, para avaliar os valores de CDA antes, durante e após 3 meses do fim do tratamento de radioquimioterapia em pacientes com câncer cervical. A intenção é que esse estudo prospectivo possa ajudar a determinar se valores de CDA aferidos em diferentes momentos do tratamento e a magnitude de sua modificação durante o curso terapêutico são fatores preditivos independentes de resposta ao tratamento, como foi sugerido por outros[99, 100].

Em resumo, os dados encontrados neste estudo corroboram com alguns relatos da literatura que apontam para a existência de correlação entre valores de CDA aferidos no tumor primário e fatores prognósticos de estadiamento como, por exemplo, a presença de linfonodos radiologicamente suspeitos para acometimento secundário. Além disso, o fato de que o CDAmín se correlacionou com piores desfechos clínicos sugere que esse parâmetro poderia ser utilizado no futuro isoladamente ou em conjunto com outros biomarcadores para estratificar pacientes e assim possibilitar a adoção de uma terapia dirigida de acordo com o prognóstico. Espera-se que a conclusão de estudos prospectivos, como o que está em andamento no Hospital de Câncer de Barretos, possam auxiliar nessa tarefa.

6. CONCLUSÕES

O CDAmáx pré-tratamento aferido no tumor primário pode estar associado com a presença de linfonodos radiologicamente suspeitos e estadiamento FIGO: valores mais elevados sugerem a presença de linfonodos acometidos e também o estadiamento mais avançado (FIGO III-IV).

O CDAmín pode ser um fator prognóstico associado a SLD e SCE em pacientes com câncer de colo de útero tratadas com radio-quimioterapia: valores mais elevados se correlacionaram com piores desfechos.

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8. ANEXOS

Anexo A - APRESENTAÇÕES EM CONGRESSOS NACIONAIS

- XIV Congresso Brasileiro de Radioterapia (São Paulo/Brasil): apresentação oral em maio/2014. Viabilidade da utilização de RNM-difusão como preditor de resposta em pacientes com câncer de colo de útero.
- XV Congresso Brasileiro de Radioterapia (Foz do Iguaçu/Brasil): apresentação oral em junho/2015. Valor máximo do coeficiente de difusão aparente pré-tratamento no Tumor primário pode predizer a presença de linfonodos radiologicamente suspeitos para acometimento secundário em pacientes com câncer do colo de útero.
- XVI Congresso Brasileiro de Radioterapia (João Pessoa, Brasil): apresentação oral em junho/2016. O valor mínimo do coeficiente de difusão aparente da RNM pré-tratamento é um potencial biomarcador prognóstico de pacientes com câncer cervical tratados com radio-quimioterapia.


XVI CONGRESSO DA SOCIEDADE
BRASILEIRA DE RADIOTERAPIA
XIV Jornada de Física Médica
XII Encontro de Enfermeiros Oncologistas em Radioterapia
XI Encontro de Técnicos em Radioterapia
V Encontro de Residentes em Radioterapia da SBRT
Sheraton São Paulo WTC Hotel
30 de abril a 3 de maio de 2014
CERTIFICADO /CERTIFICATE
Certificamos que
Daniel Grossi Marconi, José Humberto Tavares Guerreiro Fregnani, Rodrigo Ribeiro Rossini, Ana Karina Borges Junqueira Netto,
Fabiano Rubião Lucchesi, Aldrey T. Tsunomo, Mitchell Kamrava
Apresentaram o trabalho intitulado " Viabilidade da utilização de RNM-difusão como preditos de resposta em pacientes com câncer de colo de útero", na Sessão TEMAS LIVRES durante o XVI CONGRESSO DA SOCIEDADE BRASILEIRA DE RADIOTERAPIA, XIV Jornada de Física Médica, XII Encontro de Enfermeiros Oncologistas em Radioterapia, XI Encontro de Técnicos em Radioterapia, V Encontro de Residentes em Radioterapia da SBRT, realizados de 30 de Abril a 03 de Maio de 2014, no Sheraton WTC São Paulo - SP.
São Paulo, 03 de Maio de 2014.
Iniciativa e Realização
Sociedade Brasileira de Radioterapia
Robson Ferrigno
Presidente / President

CONGRESSO DA SOCIEDADE BRASILEIRA DE RADIOTERAPIA

XVII

17 A 20 JUNHO 2015

FOZ DO IGUAÇU - PR

XV Jornada de Física Médica

XIII Encontro de Enfermeiros Oncologistas em Radioterapia

XII Encontro de Técnicos em Radioterapia

VI Encontro de Residentes em Radioterapia da SBRT

CERTIFICADO /CERTIFICATE

Certificamos que

Erick Franz Rauber, Daniel Grossi Marconi, José Humberto Tavares Guerreiro Fregnani, Rodrigo Ribeiro Rossini, Ana Karina Borges Junqueira Netto, Fabiano Rubião Lucchesi, Aldrey T. Tsunomo, Mitchell Kamrava

Apresentaram o Trabalho com o Tema: "**Valor máximo do coeficiente de difusão aparente pré-tratamento no Tumor primário pode predizer a presença de linfonodos radiologicamente suspeitos para acometimento secundário em pacientes com câncer do colo de útero**", na Sessão TEMAS LIVRES durante o **XVII CONGRESSO DA SOCIEDADE BRASILEIRA DE RADIOTERAPIA, XV Jornada de Física Médica, XIII Encontro de Enfermeiros Oncologistas em Radioterapia, XII Encontro de Técnicos em Radioterapia e VI Encontro de Residentes em Radioterapia da SBRT**, realizados no período de **17 à 20 de Junho de 2015**, no Bourbon Cataratas Convention & Spa Resort, em Foz do Iguaçu – PR.

Foz do Iguaçu, 20 de junho de 2015

Iniciativa e Realização
Initiative and Realization

Sociedade Brasileira de Radioterapia

Gustavo Nader Marta
Secretário Geral da SBRT
Secretary General of SBRT

Eduardo Weltman
Presidente / *President*

CERTIFICADO / *CERTIFICATE*

Certificamos que

Daniel Grossi Marconi, José Humberto Tavares Guerreiro Fregnani, Rodrigo Ribeiro Rossini, Ana Karina Borges Junqueira Netto, Fabiano Rubião Lucchesi, Aldrey T. Tsunomo, Fernanda Buongusto, Mitchell Kamrava

Apresentaram o trabalho intitulado "**O valor mínimo do coeficiente de difusão aparente da RNM pré-tratamento é um potencial biomarcador prognóstico de pacientes com câncer cervical tratados com radio-quimioterapia**", na **Sessão TEMAS LIVRES** durante o **XVIII CONGRESSO DA SOCIEDADE BRASILEIRA DE RADIOTERAPIA**, **XVI Jornada de Física Médica, XIV Encontro de Enfermeiros Oncologistas em Radioterapia, XIII Encontro de Técnicos em Radioterapia e VII Encontro de Residentes em Radioterapia da SBRT**, realizados no período de **15 à 18 de Junho de 2016**, no Centro de Convenções de João Pessoa, em João Pessoa – PB.

João Pessoa, 18 de junho de 2016.

Iniciativa e Realização

Sociedade Brasileira de Radioterapia

Eduardo Weltman
Presidente

Gustavo Nader Marta
Secretário Geral da SBRT

Anexo B - APRESENTAÇÕES EM CONGRESSOS INTERNACIONAIS

- American Brachytherapy Society Meeting (Chicago/EUA): Apresentação Oral em julho de 2014. Diffusion Weighted Imaging and the Attenuation Diffusion Coefficient Value As A Possible Imaging Biomarker In Cervical Cancer: Correlation With Baseline Patient Characteristics.
- 57th Astro Annual Meeting, San Antonio, EUA, 2015. Poster número 2659. Pretreatment MRI Mean and Minimum Apparent Diffusion Coefficient Values Are Predictive of Treatment Response in Cervical Cancer Patients Treated With Definitive Radiation.

From: Melissa Pomerene [mailto:mpomerene@DROHANMGMT.COM] **Sent:** Tuesday, June 17, 2014 7:53 AM **To:** Kamrava, Mitchell **Cc:** Melissa Pomerene **Subject:** American Brachytherapy Society (ABS) 2014 GYN Abstract Submission

12100 Sunset Hills Road, Suite 130, Reston, VA 20190 703-234-4078 fax 703-435-4390

June 17, 2014

RE: Abstract #39

Abstract Title: **Diffusion Weighted Imaging and the Attenuation Diffusion Coefficient Value As A Possible Imaging Biomarker In Cervical Cancer: Correlation With Baseline Patient Characteristics**

Dear Dr. Kamrava:

The Program Committee of the American Brachytherapy Society (ABS) is pleased to confirm that your abstract has been accepted for an oral presentation on **Monday, July 13 from 9:00 am – 10:00 am** at the 2014 GYN School, July 12 - 14. The meeting will take place at the Westin Chicago River North.

Each presentation should be 6 minutes in length, with and additional one and a half minutes for questions. To be fair to other presenters and to keep our agenda on track, we would ask that keep your presentation within these guidelines.

Abstract Publication

Your abstract will be published in a future supplement of Brachytherapy, the official journal of the ABS.

Please indicate your acceptance by responding to this email by June 23. Please reply to this email with your acceptance.

[ ] I accept my oral presentation.

[ ] I decline my oral presentation.

Name of Presenting Author (print):_____

Signature of Presenting Author:_____

Date: _____

Audiovisual Requirements

An LCD projector, computer and laser pointer will be provided**. (Please send your presentation to Melissa Pomerene by July 7th deadline).**

Meeting Registration

Please note that all ABS member and non-member presenters must register for the

meeting and are responsible for making and paying for their travel and hotel arrangements. Information is also available on-line at www.americanbrachytherapy.org.

We look forward to seeing you in Chicago.

Sincerely,

Beth A. Erickson, MD, FACR, FASTRO Program Co-Chair Medical College of Wisconsin Akila N. Viswanathan, MD, MPH Program Co-Chair Dana-Farber Bringham and Women's Cancer Care Boston, MA

(Please send your presentation no later than **July 7)** to:

American Brachytherapy Society
12100 Sunset Hills Road, Suite 130
Reston, VA 20190
Attention: Melissa Pomerene (mpomerene@drohanmgmt.com)

Melissa Pomerene / American Brachytherapy Society / Program Manager / 12100 Sunset Hills Rd / Suite 130 / Reston, VA 20190 / Phone: (703) 234-4085 / Fax: (703) 435-4390 www.americanbrachytherapy.org

De: astro@confex.com

Data: 29 de maio de 2015 17:55:46 BRT

Para: dgmarconi@gmail.com

Assunto: ASTRO's 57th Annual Meeting - Abstract Notification

Responder A: astro@confex.com

Dear Dr. Marconi,

Congratulations! On behalf of the Annual Meeting Program Committee of the American Society for Radiation Oncology (ASTRO), it is my pleasure to inform you that your abstract has been selected for presentation in the **POSTER VIEWING** Session during the 2015 Annual Meeting being held October 18-21 in San Antonio. ASTRO has a robust Poster Hall which displays over 2,000 posters each year. It is located adjacent to the Exhibit Hall for greater exposure of your work.

Your abstract details are listed below:

Poster #: 2659

Abstract Title: Pretreatment MRI Mean and Minimum Apparent Diffusion Coefficient Values Are Predictive of Treatment Response in Cervical Cancer Patients Treated With Definitive Radiation

Presenter: Daniel Grossi Marconi

Author block: Daniel Grossi Marconi, Jose Tavares Guerreiro Fregnani, Rodrigo Ribeiro Rossini, Ana Borges Junqueira Netto, Fabiano Lucchesi, Audrey Tieko Tsunoda, Mitchell Kamrava

Poster Presenter Information

Accepted posters will be on display by disease site for the following days and times:

Sunday, October 18 10:00am – 5:00pm

Monday, October 19 10:00am – 5:00pm

Tuesday, October 20 10:00am – 5:00pm

You should plan to be onsite by Saturday, Oct. 17 or Sunday, Oct. 18 to get your poster installed in time for the 10:00am Poster Hall opening.

There will be a dedicated Poster Viewing Reception held on:

**** Monday, October 19th, from 5:30 p.m. - 6:45 p.m.**

**** At least one of the authors must be available to stand by the poster during this time for questions and answers**.

Poster Setup Times

All poster presenters must pin their poster to their poster board before the Poster Hall opens at 10:00am on Sunday, October 18th. There are two times available to do this:

Saturday, October 17 12:00 – 5:00pm

Sunday, October 18 7:30am – 10:00am

Information regarding the following details will be emailed to you by late June and will be posted on the ASTRO website:

Poster Set-up and Tear-Down Times

Poster Reception

Poster Tube Storage

Tips on Organizing Your Poster

Shipping Your Poster

Poster printing service

Housing & Registration

Housing and registration will open June 18, and can be found at:

https://www.astro.org/Meetings-and-Events/2015-Annual-Meeting/Registration-Information/Index.aspx

Nonmember abstract presenters will receive a discounted nonmember registration rate that will be applied upon registration. The discount nonmember abstract presenter rates are the following:

Early Bird (till July 30th): $760

Advance (July 31-September 17th): $810

Late (After September 17th): $885

Changes/Withdrawal

** If you have any questions regarding this notification, have any changes, or there is any reason you cannot present this abstract, or wish to withdraw your abstract from the program, you must submit your request by midnight **Tuesday, June 30** to Johanna Vanarsdall, Sr. Manager, Scientific & Education Programs - JohannaV@astro.org.

Vendor/Commercial Names

Please know that it's ASTRO's policy and in compliance with the ACCME guidelines we must avoid any commercial bias at our scientific meeting. Abstracts with vendor names or names of commercial products or services will be edited out at ASTRO's discretion. The presenting author will be notified if any edits are made and given the opportunity to comment on the changes.

Other Meetings & Publications

Should your abstract be selected for presentation at another meeting or published prior to the ASTRO Annual Meeting, please notify ASTRO staff: JohannaV@astro.org. Depending on the publication details and size of the other meeting, we may need to withdraw your abstract in order to maintain our high quality scientific program.

Questions

Should you have additional questions or concerns, please feel free to contact: JohannaV@astro.org

Congratulations on your accepted work and we look forward to seeing you in San Antonio!

Sincerely,

Benjamin Movsas, MD, FASTRO

Chairman, Annual Meeting Scientific Committee

Lisa Kachnic, MD, FASTRO

Vice-chair, Annual Meeting Scientific Committee

Anexo C - PRÊMIOS

- Primeiro lugar entre as apresentações orais do XV Congresso Brasileiro de Radioterapia em 2015 (Foz do Iguaçu/Brasil), com premiação de viagem e estadia para o maior congresso de radioterapia do mundo (ASTRO), nos EUA.
- Segundo lugar entre as apresentações orais do XVI Congresso Brasileiro de Radioterapia em 2016 (João Pessoa/Brasil).

XVII CONGRESSO DA SOCIEDADE BRASILEIRA DE RADIOTERAPIA
17 A 20 JUNHO 2015
FOZ DO IGUAÇU - PR

XV Jornada de Física Médica
XIII Encontro de Enfermeiros Oncologistas em Radioterapia
XII Encontro de Técnicos em Radioterapia
VI Encontro de Residentes em Radioterapia da SBRT

CERTIFICADO /CERTIFICATE

Certificamos que

o trabalho intitulado "**Valor máximo do coeficiente de difusão aparente pré-tratamento no Tumor primário pode predizer a presença de linfonodos radiologicamente suspeitos para acometimento secundário em pacientes com câncer do colo de útero**", de autoria de ERICK FRANZ RAUBER, DANIEL GROSSI MARCONI, JOSÉ HUMBERTO TAVARES GUERREIRO FREGNANI, RODRIGO RIBEIRO ROSSINI, ANA KARINA BORGES JUNQUEIRA NETTO, FABIANO RUBIÃO LUCCHESI, ALDREY T. TSUNOMO, MITCHELL KAMRAVA, foi premiado com **1º LUGAR** na **Sessão TEMAS LIVRES** durante o **XVII CONGRESSO DA SOCIEDADE BRASILEIRA DE RADIOTERAPIA**, **XV Jornada de Física Médica, XIII Encontro de Enfermeiros Oncologistas em Radioterapia, XII Encontro de Técnicos em Radioterapia e VI Encontro de Residentes em Radioterapia da SBRT**, realizados no período de **17 à 20 de Junho de 2015**, no Bourbon Cataratas Convention & Spa Resort, em Foz do Iguaçu – PR.

Foz do Iguaçu, 20 de junho de 2015

Iniciativa e Realização
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Sociedade Brasileira de Radioterapia

Gustavo Nader Marta
Secretário Geral da SBRT
Secretary General of SBRT

Eduardo Weltman
Presidente / *President*

CERTIFICADO / *CERTIFICATE*

Certificamos que

o trabalho intitulado "**O valor mínimo do coeficiente de difusão aparente da RNM pré-tratamento é um potencial biomarcador prognóstico de pacientes com câncer cervical tratados com radio-quimioterapia**", de autoria de **Daniel Grossi Marconi, José Humberto Tavares Guerreiro Fregnani, Rodrigo Ribeiro Rossini, Ana Karina Borges Junqueira Netto, Fabiano Rubião Lucchesi, Aldrey T. Tsunomo, Fernanda Buongusto, Mitchell Kamrava,** foi premiado com o **2º LUGAR** na Sessão **TEMAS LIVRES** durante o **XVIII CONGRESSO DA SOCIEDADE BRASILEIRA DE RADIOTERAPIA**, **XVI Jornada de Física Médica, XIV Encontro de Enfermeiros Oncologistas em Radioterapia, XIII Encontro de Técnicos em Radioterapia e VII Encontro de Residentes em Radioterapia da SBRT**, realizados no período de **15 à 18 de Junho de 2016**, no Centro de Convenções de João Pessoa, em João Pessoa – PB.

João Pessoa, 18 de junho de 2016.

Iniciativa e Realização

Sociedade Brasileira de Radioterapia

Eduardo Weltman
Presidente

Gustavo Nader Marta
Secretário Geral da SBRT

Anexo D - APROVAÇÃO NO CEP

FUNDAÇÃO PIO XII - HOSPITAL DE CÂNCER DE BARRETOS

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: VIABILIDADE DA UTILIZAÇÃO DE RNM-DIFUSÃO COMO PREDITOR DE RESPOSTA EM PACIENTES COM CÂNCER DE COLO UTERINO: UM ESTUDO

Pesquisador: Daniel Grossi Marconi

Área Temática:

Versão: 2

CAAE: 15164613.9.0000.5437

Instituição Proponente: Fundação Pio XII

Patrocinador Principal: Fundação Pio XII

DADOS DO PARECER

Número do Parecer: 264.979

Data da Relatoria: 06/05/2013

Apresentação do Projeto:

Encontra-se adequada salienta a importância do estudo principalmente em Países em desenvolvimento como Brasil e sustentando com clareza o objetivo e a necessidade do estudo.

Objetivo da Pesquisa:

Claro e bem definido.

Avaliação dos Riscos e Benefícios:

Benefícios redução de custos à metodologia padrão ouro (PET CT).

Uma previsão antecipada de resposta previamente ao inicio da terapia.

Riscos mínimos inerentes a confidencialidade dos dados.

Comentários e Considerações sobre a Pesquisa:

O estudo é possível de ser desenvolvido em nosso serviço possuindo objetivos claros.

Considerações sobre os Termos de apresentação obrigatória:

Pede dispensa do TCLE.

Recomendações:

Citar as referências no texto.

Endereço: Rua Antenor Duarte Vilela, 1331
Bairro: Dr. Paulo Prata **CEP:** 14.784-400
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Conclusões ou Pendências e Lista de Inadequações:

Foram devidamente sanadas.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

O Comitê de Ética em Pesquisa da Fundação Pio XII ¿ Hospital do Câncer de Barretos ANALISOU as pendências do referido projeto e decidindo que o mesmo encontra-se APROVADO.

Solicitamos que sejam encaminhados ao CEP:

1. Relatórios parciais previstos para 07/05/2014.
2. Os dados individuais de todas as etapas da pesquisa devem ser mantidos em local seguro por 5 anos, após conclusão da pesquisa, para possível auditoria dos órgãos competentes.
3. Este projeto está cadastrado no CEP-HCB sob o número 705/2013.

BARRETOS, 07 de Maio de 2013

Assinador por:
Ednise Woyciechowski
(Coordenador)

Anexo E - FICHA DE COLETA DE DADOS CLÍNICOS

1	Identificação	
2	Nome	
3	Registro hospitalar	
4	Data de nascimento **DD/MM/AAAA**	
5	FIGO	
6	Tamanho Tumor (RNM-1)	
7	T (RNM)	
8	N (RNM)	
9	EC (TNM)	
10	Data Biópsia **DD/MM/AAAA**	
11	Histologia **0-CEC; 1-Adenoca; 2-outros**	
12	Grau	
13	IPN **0-** Não; **1-** Sim; **99-** Ignorado	
14	IVS **0-** Não; **1-** Sim; **99-** Ignorado	
15	IVL **0-** Não; **1-** Sim; **99-** Ignorado	
16	Dose EBRT	
17	Dose HDR	
18	Data Início EBRT **DD/MM/AAAA**	
19	Data Término EBRT **DD/MM/AAAA**	
20	Data Início HDR **DD/MM/AAAA**	
21	Data Fim HDR **DD/MM/AAAA**	
22	Número Ciclos de QT	

23	Recorrência **1**-local; **2**-distant; **3**-both; **99**-Ignorado	
24	Recorrência 1-Sim; 2-Não; 3-Não se aplica	
25	Data Recorrência Dd/mm/aaaa	
26	Local 1-Sim; 2-Não; 3-Não se aplica	
27	Regional 1-Sim; 2-Não; 3-Não se aplica	
28	Distância 1-Sim; 2-Não; 3-Não se aplica	
29	Tratamento da recorrência 1-Sim; 2-Não; 3-Não se aplica	
30	RT na recorrência 1-Sim; 2-Não; 3-Não se aplica	
31	CX na recorrência 1-Sim; 2-Não; 3-Não se aplica	
32	QT na recorrência 1-Sim; 2-Não; 3-Não se aplica	
33	Tipo de QT na recorrência 1-CDDP apenas; 2-CDDP+outras drogas; 3-Outros	
34	Data do último Follow-Up Dd/mm/aaaa	
35	Status no último FU 1-Vivo sem CA; 2-Vivo com CA; 3-Morto por câncer; 4-Morte não relacionada ao CA	

Anexo F - FICHA DE COLETA DE DADOS RADIOLÓGICOS

1	Data RNM-1 **DD/MM/AAAA**	
2	Data RNM-2 se houver **DD/MM/AAAA**	
3	Tamanho Inicial do Tumor (APxCCxLL) **cm**	
4	$ADC_{mín}$ Pré-tto	
5	$ADC_{méd}$ Pré-tto	
6	$ADC_{máx}$ Pré-tto	
7	Invasão miométrio **1 – Sim; 2 – Não**	
8	Invasão cavidade endometrial **1 – Sim; 2 – Não**	
9	Invasão paramétrio **1 – Sim; 2 – Não**	
10	RNM na Recorrência **1-Sim; 2-Não; 3-Não se aplica**	
11	Invasão vagina **1 – Sim; 2 – Não**	
12	Invasão estruturas adjacentes **1 – Sim; 2 – Não**	
13	Aparelho **1 – 1,5T; 2 – 3T**	
14	FOV	
15	b-valor	
16	Espessura do corte **mm**	
17	Linfonodo suspeito **1 – Sim; 2 – Não**	

Anexo G - SITUAÇÃO DO ARTIGO

Marconi et al. BMC Cancer (2016) 16:556
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BMC Cancer

RESEARCH ARTICLE Open Access

Pre-treatment MRI minimum apparent diffusion coefficient value is a potential prognostic imaging biomarker in cervical cancer patients treated with definitive chemoradiation

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Abstract

Background: Diffusion Weighted (DW) Magnetic Resonance Imaging (MRI) has been studied in several cancers including cervical cancer. This study was designed to investigate the association of DW-MRI parameters with baseline clinical features and clinical outcomes (local regional control (LRC), disease free survival (DFS) and disease specific survival (DSS)) in cervical cancer patients treated with definitive chemoradiation.

Methods : This was a retrospective study approved by an institutional review board that included 66 women with cervical cancer treated with definitive chemoradiation who underwent pre-treatment MRI at our institution between 2012 and 2013. A region of interest (ROI) was manually drawn by one of three radiologists with experience in pelvic imaging on a single axial CT slice encompassing the widest diameter of the cervical tumor while excluding areas of necrosis. The following apparent diffusion coefficient (ADC) values ($\times 10^{-3}$ mm^2/s) were extracted for each ROI: Minimum - ADC_{min}, Maximum - ADC_{max}, Mean - ADC_{mean}, and Standard Deviation of the ADC - ADC_{dev}. Receiver operating characteristic (ROC) curves were built to choose the most accurate cut off value for each ADC value. Correlation between imaging metrics and baseline clinical features were evaluated using the Mann Whitney test. Confirmatory multi-variate Cox modeling was used to test associations with LRC (adjusted by gross tumor volume – GTV), DFS and DSS (both adjusted by FIGO stage). Kaplan Meyer curves were built for DFS and DSS. A p-value < 0.05 was considered significant.
Women median age was 52 years (range 23–90). 67 % had FIGO stage I-II disease while 33 % had FIGO stage III-IV disease. Eighty-two percent had squamous cell cancer. Eighty-eight percent received concurrent cisplatin chemotherapy with radiation. Median EQD2 of external beam and brachytherapy was 82.2 Gy (range 74–84).

Results: Women with disease staged III-IV (FIGO) had significantly higher mean ADC_{max} values compared with those with stage I-II (1.806 (0.4) vs 1.485 (0.4), $p = 0.01$). Patients with imaging defined positive nodes also had significantly higher mean (±SD) ADC_{max} values compared with lymph node negative patients (1.995 (0.3) vs 1.551 (0.5), $p = 0.03$). With a median follow-up of 32 months (range 5–43) 11 patients (17 %) have developed recurrent disease and 8 (12 %) have died because of cervical cancer. ROC curves based on DSS showed optimal cutoffs for ADC_{min} (0.488×10^{-3}), ADC_{mean} (0.827×10^{-3}), ADC_{max} (1.838×10^{-3}) and ADC_{dev} (0.148×10^{-3}). ADC_{min} higher than the cutoff was
(Continued on next page)

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(Continued from previous page)
significantly associated with worse DFS (HR = 3.632–95 % CI: 1.094–12.054; $p = 0.035$) and DSS (HR = 4.401–95 % CI: 1.048–18.483; $p = 0.043$).

Conclusion: Pre-treatment ADC_{max} measured in the primary tumor may be associated with FIGO stage and lymph node status. Pre-treatment ADC_{min} may be a prognostic factor associated with disease-free survival and disease-specific survival in cervical cancer patients treated with definitive chemoradiation. Prospective validation of these findings is currently ongoing.

Keywords: Cervical cancer, Diffusion weighted imaging, Chemoradiation, MRI

Background

In Brazil, it is estimated that 18,500 women are diagnosed with cervical cancer annually, and 8,400 die [1]. While screening rates for cervical cancer have improved in many countries, there are still a significant number of women who present with locally advanced disease that will require definitive treatment with chemoradiation. Advances in image-guided brachytherapy using Magnetic Resonance Imaging/planning (MRI) rather than 2-dimmensional techniques is significantly improving the outcomes, and changing their patterns of recurrence [2]. With image-based brachytherapy the vast majority of these patients are achieving local control of their tumors with limited serious acute or late morbidity. More women are now recurring with distant rather than local failures with marginal outcomes with systemic therapy in these cases [3]. Efforts are now underway on the OUTBACK trial [4], for example, to potentially improve these clinical outcomes with the addition of systemic chemotherapy following the completion of definitive chemoradiation. One of the challenges of this approach is being able to identify patients at highest risk for poor outcomes following chemoradiation alone. Advances in functional imaging with Positron Emission Tomography (PET) and quantification of a standardized uptake value (SUV) can provide prognostic information that may be helpful in identifying women populations at higher risk of failure, thereby allowing for an enriched patient population that is more likely to benefit from escalated therapy [5–7].

In low-middle income countries there are a limited number of cyclotrons available for PET imaging making it impossible to integrate this technology into the routine management of cervical cancer patients. MRI is, however, readily available and routinely utilized for cervical cancer staging in many countries but standard imaging sequences only provide anatomical, and not functional, information. Newer MRI sequences such as diffusion-weighted imaging (DWI) provide functional information by characterizing the diffusion of water between cells [8–10]. This can be quantitated, similar to an SUV on PET scans, by calculating an apparent diffusion coefficient (ADC) value. Previous investigators have demonstrated high concordance of tumor sub volumes with increased metabolic activity on PET with increased cellular density on DWI imaging suggesting ADC values may have similar prognostic value as SUV_{max} [8, 11].

DWI imaging has previously been studied in cervical cancer patients with mixed results regarding its utilization as a prognostic/predictive marker [12–14, 15–18]. Given the variation in correlations with DWI imaging, we investigated whether baseline MRI DWI imaging features correlate with clinical outcomes in women with locally advanced cervical cancer treated with definitive chemoradiation.

Methods

This was a retrospective study of cervical cancer women treated at Barretos Cancer Hospital, approved by the Research Ethics Committee. Patients were treated using radiation therapy with or without concurrent chemotherapy and who had an MRI of the pelvis performed prior to the start of treatment between January 2012 and March of 2013. A total of 135 patients were identified. Forty-six were excluded from further analysis because either their MRI was not performed at our institution or diffusion weighted imaging was not performed. Ten additional women were excluded because they were treated with palliative intent and 13 more were excluded because they did not have sufficient clinical follow-up information available. This left 66 women available for complete analysis.

The study group was classified according to the revised 2009 FIGO staging system. The extent of tumor involvement was based on both clinical examination and MRI findings (i.e. a patient with parametrial involvement on clinical examination but clear involvement on MRI imaging to the pelvic sidewall was classified as FIGO Stage IIIB). Positive lymph nodes were based on MRI findings. A lymph node was considered positive if it had a maximum diameter larger than 1 cm with heterogeneity of signal or an irregular contour. Enlarged lymph nodes were not routinely pathologically confirmed.

Eight patients received radiation alone and 58 were treated with chemoradiation. All 66 women received high dose rate (HDR) brachytherapy as a component of their treatment. The mean (SD) external beam and HDR doses were: 44.92 (0.62) Gy and 27.05 (1.67) Gy (7 Gy × 4 being the most common fractionation), respectively. The mean (SD) equivalent dose in 2-Gy fractions (EQD2) for external

beam plus HDR-brachytherapy was 82.2 (2.8) Gy. There was no lymph node boost.

Radiation was delivered using a standard linear accelerator with either 6MV or 15MV beams and planned using a 3D planning method with organ at risk and target volumes contoured by a radiation oncologist. Intensity modulated radiation therapy was not used. All patients were planned using Eclipse version 8.0 (Varian Medical Systems, Palo Alto, CA, USA).

For the brachytherapy, four fractions of HDR using a tandem and ovoid applicator were delivered to all patients (except two that only received three fractions of 7 Gy). The dose was prescribed to point A and was planned based on 2-dimmensional films. Bladder and rectal points were placed as per ICRU 38 guidelines. The constraints for a prescription of 7 Gy were 71 % (bladder) and 58 % (rectum). Dose prescription was diminished to 6.5 Gy or 6 Gy when the constraints were extrapolated. Brachytherapy planning was performed using GammaMed™ (Varian Medical Systems Inc., Palo Alto, CA, USA).

The majority of women (82 %) were treated with concurrent cisplatin chemotherapy at a dose of 40 mg/m^2 weekly. Four women received concurrent carboplatin and eight did not receive concurrent chemotherapy.

All patients were followed up with physical exam, abdominal/pelvic imaging and surveillance pap smears every 3 to 6 months.

Disease recurrence was determined radiographically by RECIST 1.1 criteria [19] and was not pathologically confirmed. Local regional control was defined as the time from biopsy to local (uterine cervix or vagina) or regional recurrence (pelvic lymph node). Disease free survival (DFS) was defined as the time from biopsy to tumor progression. Disease specific survival (DSS) was defined as the time between biopsy to death by cancer.

Imaging technique and analysis

All images were performed at baseline assessment (before any treatment) on one of two scanners: Achieva 3.0 Tesla, Philips Healthcare, Netherlands or a Signa HDXT 1.5 Tesla, GE Healthcare, Milwaukee. All patients had trans-vaginal ultrasound gel administered prior to the start of their MRI. The sequences acquired included T2-weighted sequences of the whole pelvis and abdominal region below the renal arteries, axial T1-weighted sequences of the whole pelvis, T2-weighted sequences in the sagittal, axial and coronal planes at an angle through the plane of the cervix, and diffusion-weighted sequences. For the diffusion sequence, the field of view was 40 × 40, the matrix size was 512, with b-values of 0, 600 (3 T scanner) and 0, 800 (1.5 T scanner). Acquisition time was 6 min. Voxel size was 2.34 mm (RL), 3.19 mm (AP). Repetition time was 1800 ms and slice thickness was 3 mm.

After generating the ADC maps, a region of interest (ROI) was manually drawn by one of three experienced radiologists (F.R.L., A.K.B.J.N., R.R.R.) on a single DWI slice that showed the lesion at its maximum diameter, using axial FSE T2WI for guidance. PACS software (PixViewer, Viewer MPR - PIXEON) then calculated the ADC minimum (ADC_{min}), mean (ADC_{mean}), maximum (ADC_{max}) and standard deviation of the ADC values (ADC_{dev}) (×10^{-3} mm^2/s) of the chosen region (Fig. 1).

Statistical considerations

The Mann Whitney test was used to compare ADC values of clinical-pathological and treatment-related factors including: FIGO stage (I/II vs III/IV), histology (squamous vs non-squamous), tumor grade (1-2 vs 3), lymph node status (N+ vs N-), parametrial invasion (yes vs no), vaginal invasion (yes vs no), rectal/bladder invasion (yes vs no), Gross Tumor Volume (GTV) (greater than or less than

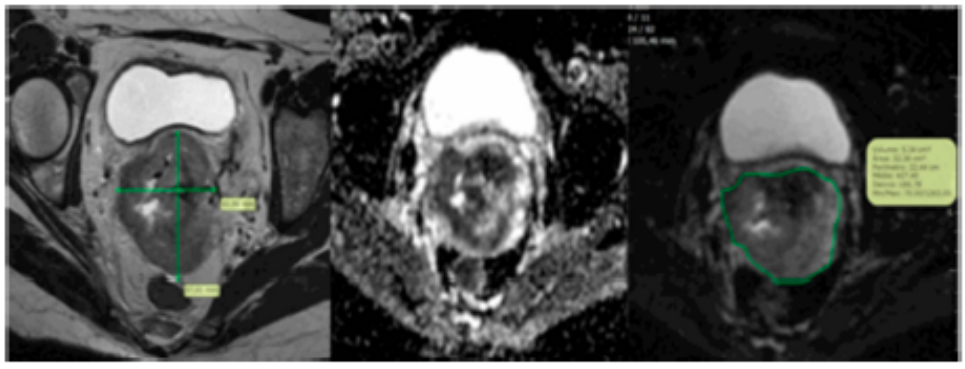

Fig. 1 Magnetic resonance imaging examples of axial slices of: T2 weighted (*left*), diffusion weighted imaging (*center*), and region of interest drawn on an attenuation diffusion coefficient map (*right*)

the median), radiation dose to the primary tumor expressed as an EQD2 (greater than or less than the median) and usage of chemotherapy (yes vs no).

ROC curves were built in order to choose a cutoff value for ADC variables. Confirmatory multivariate Cox model analysis was used to test ADC values and associations with DFS and DSS. These models were adjusted by FIGO stage. LRC was evaluated by confirmatory logistic regression using the GTV as the adjustable variable. Three-year survival rates (DFS and DSS) were estimated according to Kaplan Meyer method. Significance level was set at 5 % for all statistics.

Availability of data

The data that support our findings will not be shared due to patient privacy issues and the lack of written consent form signed by patients (retrospective study).

Results

Correlations between imaging parameters and baseline clinical features

Of the 66 women included in the analysis, 44 had FIGO stage I-II disease while 22 had stage III-IV disease. Seventy-one percent had well or moderately differentiated disease and 82 % had squamous cell cancer. Additional patient details are presented in Table 1.

Table 1 Patient and treatment characteristics

	n (%)
Number of patients	66
Median age at diagnosis (range)	51.8 (23.3–90.1)
Histology	Squamous: 54 (82 %)
	Adenocarcinoma: 7 (11 %)
	Adenosquamous: 5 (8 %)
Grade (differentiation)	Well: 4 (6 %)
	Moderate: 43 (65 %)
	Poor: 19 (29 %)
FIGO Stage (2009)	IB1-2: 2 (3 %)
	IIA1-IIB: 42 (64 %)
	IIIA-B: 16 (24 %)
	IVA-B: 6 (9 %)
Median External beam radiotherapy dose (range)	44.92 Gy (39.6-59.4)
Median HDR Brachytherapy dose (range)	27.05 Gy (21–28)
Median Total external beam and brachytherapy dose as an EQD2 (range)	82.2 Gy (74-83.9)
Concurrent chemotherapy	58 (88 %)

Table 2 shows comparisons between baseline clinical features and different ADC values. Women with FIGO stage III-IV disease had significantly higher mean ADC_{max} values compared with stage I-II (1.8 vs. 1.5, $p = 0.007$). Patients with imaging defined positive nodes also had significantly higher mean ADC_{max} values compared with lymph node negative ones (2.0 vs. 1.6, $p = 0.029$). No other significant correlations were seen.

Treatment outcomes

After a median follow up of 32 months (range 5–43), 11 patients (17 %) developed recurrent disease (from whom three were still alive by the time of the analysis) with a median time to recurrence of 9 months (range 5–39). Two patients developed pelvic recurrence only (one an in-field recurrence in the cervix and one in a left external iliac lymph node), five developed distant metastasis only, and four developed both pelvic/distant disease recurrence. For these four patients, the pelvic component of failure included: two in the cervix only and two in the

Table 2 Mean ADC values according to tumor stage, lymph node involvement, and MRI assessed disease extent

	ADC_{min}	ADC_{mean}	ADC_{max}	$ADC_{deviation}$
FIGO Stage	($p = 0.077$)	($p = 0.227$)	($p = 0.007$)	($p = 0.070$)
I-II ($n = 44$, being 22 with positive nodes)	0.375	0.855	1.485	0.224
III-IV ($n = 22$, being 18 with positive nodes)	0.267	0.901	1.806	0.256
Lymph node	($p = 0.902$)	($p = 0.092$)	($p = 0.029$)	($p = 0.154$)
Positive ($n = 40$)	0.323	0.959	1.995	0.232
Negative ($n = 26$)	0.341	0.861	1.551	0.197
Parametrial Invasion	($p = 0.680$)	($p = 0.810$)	($p = 0.081$)	($p = 0.492$)
Present ($n = 59$)	0.332	0.867	1.618	0.223
Absent ($n = 7$)	0.404	0.898	1.371	0.177
Vaginal Invasion	($p = 0.190$)	($p = 0.252$)	($p = 0.203$)	($p = 0.887$)
Present ($n = 47$)	0.311	0.848	1.624	0.198
Absent ($n = 19$)	0.410	0.925	1.513	0.267
Adjacent structure invasion (rectum or bladder)	($p = 0.683$)	($p = 0.184$)	($p = 0.301$)	($p = 0.829$)
Present ($n = 21$)	0.353	0.904	1.702	0.192
Absent ($n = 45$)	0.339	0.854	1.542	0.231
Gross tumor volume (cc)[a]	($p = 0.172$)	($p = 0.886$)	($p = 0.147$)	($p = 0.468$)
> 114.48	0.295	0.862	1.674	0.237
< 114.48	0.383	0.877	1.508	0.206

[a]Calculated by multiplication of the tumor measures (left-right, anterior-posterior, cranial-caudal)

cervix and pelvic lymph nodes. Six out of eight women did not receive concurrent chemo (and were free of disease by the time of the analysis.

There have been a total of nine deaths in the 66 women with a median time to death of 13 months (range 9–32). Eight patients (12 % of the total 66) have died from cervical cancer (they presented cancer recurrence) and one patient died from a pulmonary embolus who had no evidence of disease at the time of death. Baseline clinical features of the eight patients who died from cervical cancer include: median age 57 (range 36–74), 6/8 SCC, 8/8 moderate/poorly differentiated, 6/8 FIGO stage III-IV, 6/8 received chemotherapy, median GTV volume 154 cc, and median EQD2 of external beam and brachytherapy was 82 Gy (range 74–83.9).

The 3-year LRC and DFS for the entire group were 89.3 and 84.8 %, respectively. The 3-year DSS was 87.5 %. Table 3 shows the univariate analysis for correlation between clinical characteristics with DFS and DSS.

Cutoff points for predicting the analyzed outcomes were chosen by ROC curve analysis for ADC_{min} (0.488 × 10^{-3} mm^2/s, AUC = 0.57; 95 % CI: 0.33–0.79), ADC_{mean} (0.827 × 10^{-3} mm^2/s, AUC = 0.72; 95 % CI: 0.56–0.88), ADC_{max} (1.838 × 10^{-3} mm^2/s, AUC = 0.70; 95 % CI: 0.50–0.90) and ADC_{dev} (0.148 × 10^{-3} mm^2/s, AUC = 0.60; 95 % CI: 0.41–0.78).

Table 3 Univariate analysis for disease specific survival and disease free survival

			Disease specific survival		Disease free survival	
Variable	Category	*n*	3-y DSS	*p*-value	3-y DFS	*p*-value
FIGO	I / II	44	95.3	0.007	90.9	0.018
	III / IV	22	72		72.7	
Lymph node	Positive	40	79.1	0.015	74.9	0.024
	Negative	26	100		100	
Parametrial Invasion	Present	59	85.9	0.304	83	0.816
	Absent	7	100		100	
Vaginal Invasion	Present	47	84.3	0.265	82.9	0.850
	Absent	19	94.7		89.5	
Adjacent Structures Invasion	Present	21	71.1	0.005	69.3	0.015
	Absent	45	95.3		93	
GTV (*)	<114.48	41	97.6	0.001	95.1	0.003
	>114.48	25	69.4		68	
ADC_{min} (*)	<0.488	45	93.1	0.060	90.9	0.073
	> 0.488	21	76.2		72.7	
ADC_{mean} (*)	< 0.827	25	100	0.017	96	0.037
	> 0.827	41	79.3		77.9	
ADC_{max} (*)	< 1.838	51	93.9	0.002	90.2	0.053
	> 1.838	15	64.6		66	
ADC_{dev} (*)	< 0.148	16	100	0.088	93.8	0.221
	> 0.148	50	83.2		81.9	

(*)Cutoff values were defined by ROC curve analysis

Tables 4 and 5 show the multivariate analysis for LRC and survival, respectively. No ADC value was correlated with LRC. ADC_{min} higher than the cut off was independently associated with worse DFS (HR = 3.6–95 % CI: 1.09–12.05; $p = 0.035$) and DSS (HR = 4.4–95 % CI: 1.05–18.5; $p = 0.043$). Figures 2 and 3 show Kaplan Meyer curves for DFS and DSS, respectively.

Discussion

Recent advances in imaging have improved the ability to characterize the full extent of local disease extension, pelvic/para aortic lymph node involvement, and the presence of distant metastasis in cervical cancer patients [11]. Functional information derived from PET/CT like the SUV_{max} can also be prognostic [5–7]. Unfortunately this advance in PET/CT imaging is not readily available in developing countries such as Brazil. MRI imaging is, however, more accessible. MRI has the advantage of providing superior soft tissue anatomy compared with CT, which in turn improves assessment of locoregional disease. In addition, functional MRI sequences have the potential to make MRI more than just an anatomic tool. Areas of interest can be contoured on DWI imagined and be quantified by calculating an ADC value. DWI imaging is also very practical in that it does not require much additional scan time or require intravenous contrast [10, 12–14].

In this study we found that pre-treatment ADC_{max} was significantly correlated with FIGO stage and radiographically enlarged lymph nodes. A recent study from Memorial Sloan Kettering Cancer Center also showed a significant

Table 4 Multivariate logistic regression models for local regional control

Variables	Category (*1)	*n*	HR (*2)	95 % CI
ADC_{min}	< 0.488	45	Ref.	
	> 0.488	21	3.9	0.6–27.7 ($p = 0.169$)
ADC_{mean}	< 0.827	25	Ref.	
	> 0.827	41	1.7	0.2–17.7 ($p = 0.650$)
ADC_{max}	< 1.838	51	Ref.	
	> 1.838	15	1.3	0.2–10.0 ($p = 0.771$)
ADC_{dev}	< 0.148	16	Ref.	
	> 0.148	50	0.9	0.1–9.7 ($p = 0.934$)

HR hazard ratio, *CI* confidence interval, *Ref* reference
(*1) Cutoff values were defined by ROC curve analysis
(*2) Each model was adjusted by Gross Tumor Volume (GTV: cutoff value = 114.48)

Table 5 Multivariate models for disease specific survival and disease free survival

			Disease specific survival		Disease free survival	
Variable	Category (*1)	N	HR (*2)	95 % CI	HR	95 % CI
	< 0.488	45	Ref		Ref	
ADC_{min}	> 0.488	21	4.4	1.1–18.5 ($p = 0.043$)	3.6	1.1–12.1 ($p = 0.035$)
	< 0.827	25	Ref		Ref	
ADC_{mean}	> 0.827	41	277.3	0.0–2.7 ($p = 0.963$)	4.9	0.6–39.5 ($p = 0.138$)
	< 1.838	51	Ref		Ref	
ADC_{max}	> 1.838	15	4.3	1.0–19.3 ($p = 0.056$)	2.1	0.6–7.3 ($p = 0.255$)
	< 0.148	16	Ref		Ref	
ADC_{dev}	> 0.148	50	202.5	0.0–2.4 ($p = 0.969$)	2.7	0.4–21.1 ($p = 0.354$)

HR hazard ratio, *CI* confidence interval, *Ref* reference
(*1) Cut-off values were defined by ROC curve analysis
(*2) Each model was adjusted by FIGO staging (I/II vs III/IV)

correlation between pretreatment ADC_{mean} with FIGO stage and the presence of positive lymph nodes [15]. However, while their study showed significantly higher ADC_{mean} for earlier staged disease and uninvolved nodes we found exactly the opposite result (higher values of ADC_{max} for higher staged disease and positive nodes). This difference demonstrates some of the challenges of comparing results between studies given non-standardized methods for calculating and reporting ADC results and is discussed further below.

Investigating whether baseline ADC values might be a prognostic imaging biomarker may be more important than a correlation with baseline tumor characteristics. If validated this would give us an opportunity to consider risk adapting patients at the start of their treatment rather than waiting until a recurrence or subjecting all patients to an increased intensity regimen, where only a few might actually benefit. Whether ADC values are prognostic, similar to SUV_{max}, is an area of active investigation with existing publications showing both increased and decreased pre-treatment ADC tumor values correlating with clinical outcomes [20–22].

The literature to date using ADC for assessing prognosis has predominantly focused on metrics such as ADC_{min}, ADC_{max}, ADC_{mean}, and ADC percentiles when a histogram-based analysis is used. One recent histogram based analysis includes a recent study of 85 cervical cancer women treated with chemoradiation demonstrating a lower baseline absolute and normalized ADC 95th percentile is associated with shorter disease free survival on multivariate analysis [16]. Other groups have reported on using ADC information gleaned from a single MRI slice. In one retrospective study of 45 cervical cancer women treated with a mix of definitive surgery and chemoradiation, a lower pretreatment ADC_{mean} was predictive of

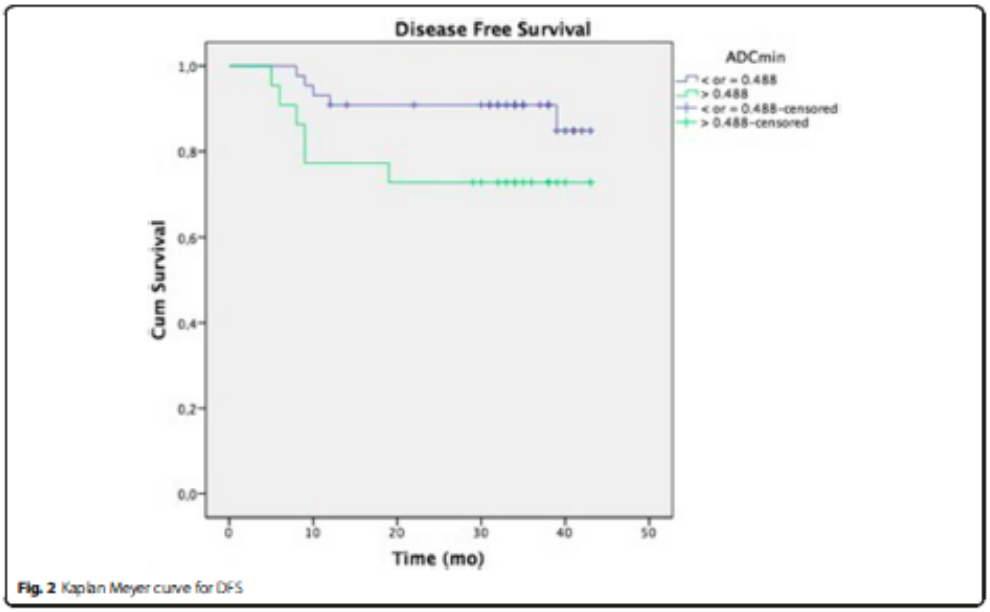

Fig. 2 Kaplan Meyer curve for DFS

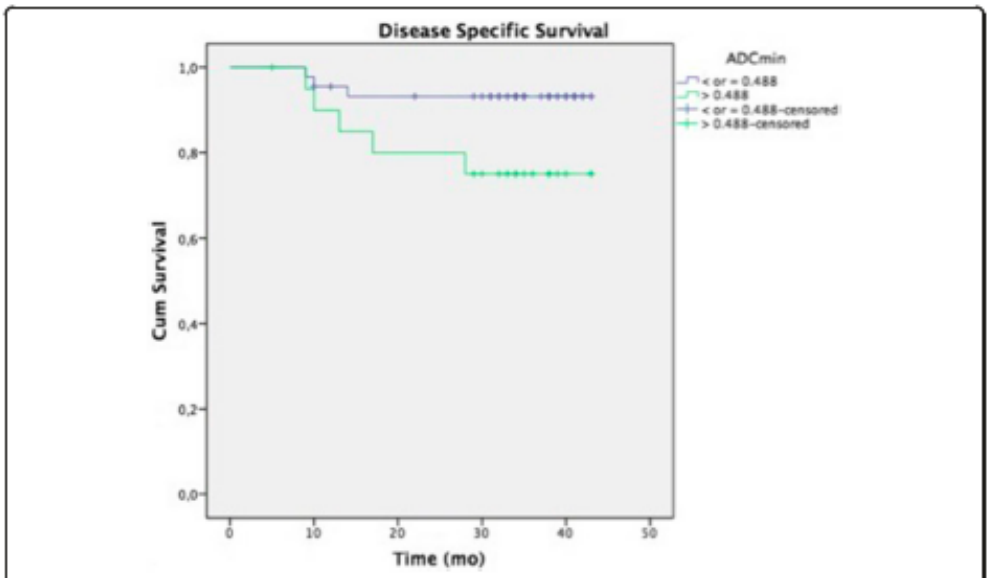

Fig. 3 Kaplan Meyer curve for DSS

both disease free and overall survival [15]. While these are two of the larger studies published to date looking at correlations between ADC values and clinical outcomes in cervical cancer, there are multiple studies that have been published on this topic with variation in the correlation between ADC values and outcomes. Some studies have correlated higher pre-treatment ADC values with inferior outcomes, while others have correlated lower pre-treatment values with inferior outcomes. These inconsistencies are likely related to multiple factors including: the heterogeneity of the patients, different treatments (surgery vs chemoradiation), various histologies (squamous cell cancer vs adenocarcinoma), use of a single slice region of interests for calculating ADC values which can underestimate the true heterogeneity of the overall tumor, different MRI imaging protocols, retrospective study design, different time points for assessing treatment response, and small patient numbers. These discrepancies point to some of the challenges in comparing data across various studies. Moving forward there needs to be agreed upon imaging and reporting standards so that data can be compared across different institutions. This is not a problem unique to DWI and similar discrepancies have been reported for dynamic contrast enhanced MRI studies in cervical cancer [17].

We looked at standard ADC metrics like the minimum, maximum and mean but also evaluated the ADC_{dev}, which has not been previously reported on. ADC_{min} and ADC_{max} represent extreme values that can be very sensitive to tumor composition, i.e., extremely high or extremely low ADC sub-volumes (which could have prognostic value). The fact that ADC_{mean} represents a much larger amount of information (it represents the mean value of all voxels measures including the ADC_{min} and ADC_{max}) could explain the observation that it reached significance only in the univariate analysis but didn't do in the multivariate where only ADC_{min} was significantly associated to outcomes - higher values were correlated with poorer DSS and DFS. A number of studies have linked ADC values to therapy outcomes, with most of them showing that tumors with higher values respond less favorably to therapy [23–27] . Mechanistically this may be explained by the presence of microscopic and macroscopic tumoral necrosis, which can increase ADC values and is linked to poorer outcomes [18, 28]. Our data is in contrast however to Nakamura et al. [29] who analyzed the combination of ADC_{min} and SUV_{max} in 66 women with cervical cancer. Women with lower ADC_{min} showed decreased OS compared to those with the highest values. The fact that we found exactly the opposite in our study (highest values of ADC_{min} predicting worse DSS) only exemplifies the difficulties in interpreting this data without standardized reporting.

When looking at the makeup of the patients who died from cervical cancer one can see that although the majority had advanced features (FIGO III/IV disease,

moderate/poorly differentiated SCC, and large GTV volumes) that there were many patients with similar features who had positive outcomes. This emphasizes the limitations of our current risk stratification schemes that focus on clinical and pathologic features without integrating information about the biology of the tumors. While the underlying biology responsible for variations in ADC values in cervical cancer is not known it does provide functional information that is currently not incorporated into our standard risk stratification tools. Given that the dominant pattern of failure in our cohort included a component of distant failure (nine out of 11 cases) it is critical that we identify women at high risk of distant failure as early on in the natural history of their disease as possible in an effort to improve their outcomes. With additional data it's possible that information gleaned from functional imaging could help identify high risk populations either independently or synergistically with our current clinically based stratification.

There are some weaknesses of our study which include its retrospective design. This contributes to differences in the timing and method of assessment of clinical response as well as the different b-values used for the DWI studies. Variation in b-values occurred due to the adoption of different imaging protocols over time. A study published by Hoogendam et al. however reported that changing the tested b-value combinations did not influence the ADC-based differentiation of benign tissue from malignant tissue and so it is not clear if this impacted the results of this study [30]. Also, we limited the number of adjusted variables in the confirmatory multivariate model in order to avoid an over fitting due to the relative small number of events [31]. Hence, we decided to use well-known prognostic factors as adjusted variables such as FIGO stage for DSS and DFS and GTV for LRC. Moreover, patients were treated using 2-dimmentional brachytherapy and did not have their enlarged lymph nodes boosted. This might have impacted the patterns of failure and ultimate treatment outcomes as has been suggested by the improved outcomes using 3-dimmentional image guided brachytherapy data, however, the local failure rates in this series are low and the predominant failure pattern was distant which is in line with more modern image guided outcomes.

These findings need to be validated in a prospective setting and we have already open a clinical trial measuring ADC values at baseline, mid-treatment, and 3 months post-treatment in patients being treated with chemoradiation for cervical cancer. Ultimately a prospective trial will help determine whether baseline or mid-treatment MRI features, as has been suggested by others are independent predictors of outcomes and whether this could be used for selecting patients that may benefit from escalated treatment [32, 33].

Conclusions

Pre-treatment ADC_{max} measured in the primary tumor may be associated with FIGO stage and lymph node status. Higher pre-treatment ADC_{min} measured in the primary tumor of cervical cancer might predict worse disease free survival and disease specific survival in patients treated with definitive chemoradiation. Prospective validation of these findings is currently ongoing.

Abbreviations

ADC, apparent diffusion coefficient; ADCdev, standard deviation of the ADC; ADCmax, maximum value of ADC; ADCmean, mean value of ADC; ADCmin, minimum value of ADC; AUC, area under curve; CI, confidence interval; DFS, disease free survival; DSS, disease specific survival; DW, diffusion weighted; HDR, high dose rate; HR, hazard ratio; LRC, local regional control; MRI, magnetic resonance imaging; PET, positron emission tomography; ROC, receiver operating characteristic; ROI, region of interest; SCC, squamous cell carcinoma; SD, standard deviation; SUV, standardized uptake value

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Availability of data and materials

The datasets generated during and/or analysed during the current study are not publicly available due to confidentially reasons but are available from the corresponding author on reasonable request.

Authors' contributions

DGM discussed the initial purpose of the study (conception, design), collected clinical data and drafted the manuscript. JHTGF discussed the initial purpose of the study (conception, design), performed the statistical analysis and drafted the paper. RRR discussed the initial purpose of the study (conception, design), collected radiological data and drafted the manuscript. AKBJN discussed the initial purpose of the study (conception, design), collected radiological data and drafted the manuscript. FRL discussed the initial purpose of the study (conception, design), collected radiological data and drafted the manuscript. ATT discussed the initial purpose of the study (conception, design) and drafted the manuscript. MK discussed the initial purpose of the study and drafted the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

As a retrospective study, consent inform was not given to patients. However, patient records/information was anonymized and de-identified prior to analysis. It was approved by the Barretos Cancer Hospital Institutional Review Board.

Research involving animals

Not applicable.

Research involving plants

Not applicable.

Trial registration

Not applicable.

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