ANÁLISE CLÍNICO-DOSIMÉTRICA DA DOSE EM BEXIGA E RETO NA BRAQUITERAPIA GINECOLÓGICA DE ALTA TAXA DE DOSE BASEADA EM PLANEJAMENTO EM TRÊS DIMENSÕES

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Orientador: Dr. Glauco Baiocchi Neto

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DEDICATÓRIA

Dedico esta tese a Deus, a minha família e as pacientes envolvidas.

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RESUMO

Sapienza LG. **Análise clínico-dosimétrica da dose em bexiga e reto na braquiterapia ginecológica de alta taxa de dose baseada em planejamento em três dimensões.** São Paulo; 2018. [Tese de Doutorado-Fundação Antônio Prudente].

Novas perspectivas no campo da braquiterapia abriram-se com a disseminação dos métodos de imagem tridimensionais ocorrida nas últimas décadas. No contexto específico da braquiterapia de cúpula vaginal, este estudo teve por objetivo avaliar a reprodutibilidade e a relação entre parâmetros de dose em órgãos de risco com a incidência de toxicidade aguda nos sistemas urinário e intestinal. Foi observada uma falta de reprodutibilidade dos parâmetros de dose pontuais de bexiga (D_{MAX} e D_{ICRU}) após a alteração da tensão aplicada sobre o cateter de Foley na via urinária da paciente. Além disso, foi constatado que múltiplos parâmetros dosimétricos de órgãos como bexiga, uretra, trígono vesical foram relacionados com a incidência de toxicidade urinaria, bem como parâmetros dosimétricos do reto e cólon sigmoide foram relacionados com a incidência de toxicidade retal.

SUMMARY

Sapienza LG. **[Clinical-dosimetric analysis of the dose in the bladder and rectum in high dose rate gynecological brachytherapy based on three-dimensional planning]**. São Paulo; 2018. [Tese de Doutorado-Fundação Antônio Prudente].

New perspectives in the field of brachytherapy have opened up with the dissemination of three-dimensional imaging methods that have occurred in the last decades. In the specific context of vaginal vault brachytherapy, this study aimed to evaluate the reproducibility and the relation between dose parameters in organs at risk with the incidence of acute toxicity in the urinary and intestinal systems. A lack of reproducibility of the bladder-specific dose-dependent parameters (D_{MAX} e D_{ICRU}) was found after a change in the tension applied on the Foley catheter in the urinary tract of the patient. In addition, it was found that multiple dosimetric parameters of organs such as the bladder, urethra, and the bladder trigone were related to the incidence of urinary toxicity. The dosimetric parameters of the rectum and sigmoid colon were related to the incidence of rectal toxicity.

LISTA DE ABREVIAÇÕES

ABS	*American Brachytherapy Society*
AP	anteroposterior
BCV	braquiterapia de cúpula vaginal
BED	*biological equivalent dose* (dose biológica equivalente)
CA	California
Cc	centímetro cúbico
cm	centímetro
ESTRO	*European Society for Radiotherapy and Oncology*
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
GEC	*Groupe Européen de Curiethérapie*
ICRU	*International Commission on Radiation Units and Measurements*
LDR	*low dose rate* (baixa taxa de dose)
ODR	órgãos de risco
PORTEC	*Post-Operative Radiation Therapy for Endometrial Carcinoma*
RIA	risco intermediário alto
RIB	risco intermediário baixo
RTE	radioterapia externa
RTOG	*Radiation Therapy Oncology Group*
USA	*The United States of America*

ÍNDICE

1 INTRODUÇÃO

Braquiterapia de cúpula vaginal (BCV) com ou sem radioterapia externa (RTE) é um componente integral do tratamento adjuvante do câncer de endométrio (KLOPP et al. 2014), e essa combinação é uma opção para alguns casos de câncer de colo uterino (CHEN et al. 2007).

A documentação da dose nos órgãos de risco (ODR) durante a braquiterapia ginecológica intracavitária foi formalmente padronizada em 1985 pelo relatório 38 da *International Commission on Radiation Units and Measurements* (ICRU 1985). Este documento sugere que as doses na bexiga e reto sejam reportadas utilizando pontos de referência, visualizados em radiografias ortogonais simples. (Figura 1).

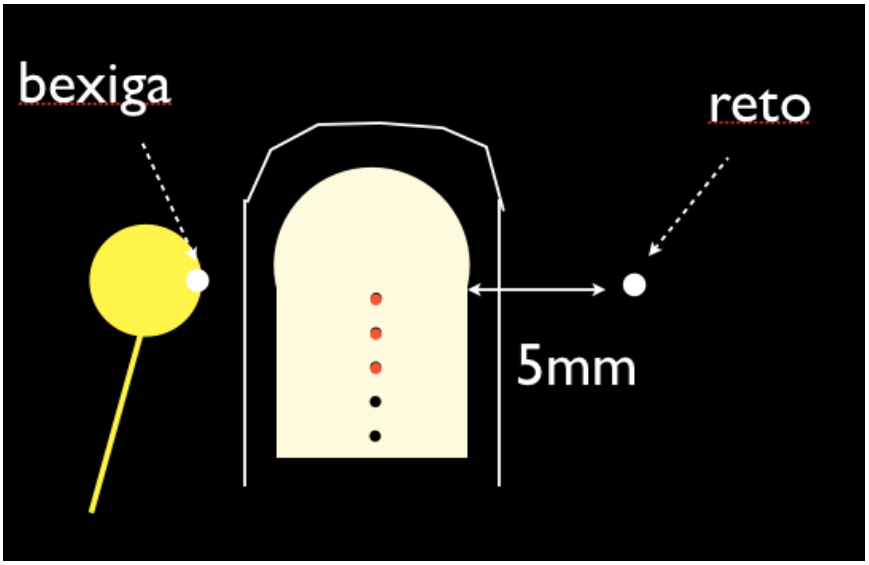

Figura 1 - Pontos de referência ICRU 38. ponto Reto: 0.5cm posterior do cilindro / Bexiga: na parte central-posterior do balão de sondagem vesical.

Publicadas em 2006, as recomendações direcionadas para braquiterapia de colo uterino baseada em imagens tridimensionais (3D) combinadas do *Groupe Européen de Curiethérapie* (GEC) e da *European Society for Radiotherapy and Oncology* (ESTRO) (PÖTTER et al. 2006), advogam a documentação da dose na bexiga com os pontos ICRU de referência e dos seguintes parâmetros volumétricos: dose mínima nos volumes de 0,1 cm, 1,0 cm e 2,0 cm com maior dose. Em 2012, a *American Brachytherapy Society* (ABS) publicou um consenso de recomendações para BCV (SMALL et al. 2012), que incluem a necessidade de reportar as doses em órgãos adjacentes, particularmente a bexiga e o reto, mas não especifica exatamente quais parâmetros utilizar. O recente relatório número 89 da ICRU (ICRU 2016) sugere que o padrão mínimo para reportar a dose deve conter os pontos de referência ICRU e a dose mínima nos 0.1 cc e 2.0 cc da bexiga e do reto.

Atualmente, a escolha entre os parâmetros de dose pontuais, como o ponto de bexiga indicado pelo ICRU (D_{ICRU}) ou o ponto de dose máxima da bexiga (D_{MAX}), e os parâmetros volumétricos, se suporta apenas em estudos dosimétricos (BARNEY et al. 2007; STEWART et al. 2008; HOLLOWAY et al. 2011; RUSSO et al. 2012; HUNG et al. 2012, CAON et al. 2014; SABATER et al. 2015). Muitos estudos têm comparado a dose no ponto ICRU e alguns parâmetros volumétricos, mas a falta de relação entre eles e a toxicidade dificulta que um seja escolhido como padrão em detrimento do outro. Deste modo, algum grau maior de evidencia da superioridade do planejamento 3D em relação à capacidade de prever toxicidade sobre o

planejamento 2D, ou alguma limitação técnica não antes documentada do planejamento 2D, deve ser demonstrada para justificar a utilização dos parâmetros volumétricos no cenário pós-histerectomia.

Na braquiterapia de baixa taxa de dose (LDR), por exemplo, foi demonstrada falta de correlação entre a dose no ponto de referencia do reto e a incidência de toxicidade tardia grau 2 reto-sigmoide, bem como entre a dose no ponto ICRU de bexiga e a toxicidade urinária grau 2 ou 3 (PEREZ et al. 1999). Até então, nenhum estudo examinou a relação clinica dos pontos ICRU e a sua capacidade de predizer toxicidade no tratamento com braquiterapia de alta taxa de dose de fundo vaginal.

A partir de uma coorte retrospectiva (parte I) e do recrutamento de pacientes num estudo prospectivo (partes II e III), objetivamos a coleta de dados clínico-dosimétricos de pacientes atendidas pelo Departamento de Radio-Oncologia do A. C. Camargo Cancer Center, tentaremos demonstrar as limitações da dosimetria convencional (2D) e avaliaremos se a dosimetria trimensional se relaciona mais fidedignamente com a ocorrência de efeitos adversos.

2 OBJETIVOS

2.1 OBJETIVO GERAL

Demonstrar as limitações da dosimetria convencional (2D) no tratamento adjuvante de braquiterapia e avaliar se a dosimetria volumétrica (3D) se relaciona mais fidedignamente com a ocorrência de efeitos adversos.

2.2 OBJETIVOS ESPECÍFICOS PARTE I

IA) Obter dados de incidência de toxicidade aguda urinária e intestinal numa coorte retrospectiva de pacientes tratadas no Departamento de Radioterapia do A. C. Camargo Cancer Center

IB) Comparar a dose no ponto ICRU bexiga das pacientes supracitadas com e sem toxicidade aguda urinária

IC) Obter resultados oncológicos de controle local e sobrevida global das pacientes supracitadas

2.3 OBJETIVOS ESPECÍFICOS PARTE II

IIA) Obter dados de dose volumétricos (3D) e pontuais (2D) da bexiga em dois níveis de tração do cateter de Foley numa coorte prospectiva de pacientes tratadas no Departamento de Radioterapia do A. C. Camargo Cancer Center

IIB) Quantificar o deslocamento do balão do cateter de Foley utilizado

IIC) Comparar a reprodutibilidade da dose nos parâmetros supracitados nos dois níveis de tensão do cateter de Foley

IID) Comparar a dose reportada nos parâmetros supracitados, com a mesma tensão sobre o cateter de Foley

2.4 OBJETIVOS ESPECÍFICOS PARTE III

IIIA) Obter dados de dose volumétricos (3D) e pontuais (2D) do trígono vesical, uretra, reto e cólon sigmoide numa coorte prospectiva de pacientes tratadas no Departamento de Radioterapia do A. C. Camargo Cancer Center

IIIB) Comparar a dose reportada nos parâmetros supracitados para cada órgão separadamente

IIIC) Obter dados quantitativos e qualitativos acerca da toxicidade aguda urinária e intestinal na coorte prospectiva supracitada

IIID) Relacionar faixas de dose em cada estrutura do sistema urinário estudado com a ocorrência de eventos de toxicidade aguda urinária

IIIE) Relacionar faixas de dose em cada estrutura do sistema intestinal estudado com a ocorrência de eventos de toxicidade aguda intestinal

IIIF) Relacionar outros parâmetros relacionadas a paciente e ao tratamento com a ocorrência de eventos de toxicidade aguda urinária e intestinal

3 METODOLOGIA

3.1 METODOLOGIA PARTE I

3.1.1 Critérios de elegibilidade

Esta parte do estudo envolveu pacientes com diagnóstico de câncer de endométrio que foram inicialmente tratadas no período entre 2009 e 2013 com ressecção cirúrgica completa e estadiamento, e foram classificadas como estagio clínico I, doença de risco intermediário. Este período foi selecionado pois ocorreram mudanças nas diretrizes departamentais após a divulgação dos resultados do estudo PORTEC-2 (NOUT et al. 2010), com a redução do uso da radioterapia externa pélvica das pacientes com câncer de endométrio estagio I de risco intermediário. Deste modo, a partir deste período, estas pacientes começaram a ser tratadas apenas com braquiterapia de fundo vaginal.

As pacientes foram divididas em dois subgrupos. O grupo de risco intermediário alto (RIA) foi baseado nos critérios de elegibilidade do estudo PORTEC-2: idade maior que 60 anos e estagio FIGO 2009 IB (invasão de mais de 50% do miométrio) com grau histológico 1 ou 2; estagio FIGO 2009 IA (invasão de menor ou igual a 50% do miométrio) com tumor grau 3; e estagio IIA e qualquer idade (exceto grau histológico 3 com mais de 50% de invasão do miométrio). O restante das pacientes foi classificado como risco intermediário baixo (RIB), excluindo-se os cases IA G1 sem fatores

patológicos adversos, como invasão vásculo-linfática ou envolvimento do istmo.

3.1.2 Dosimetria e Tratamento

Os dados dosimétricos foram obtidos no sistema de planejamento de tratamento (Eclipse®, version 11.0, Varian, Palo Alto, CA, USA) a partir de imagens de radiografia ortogonais simples. Os pontos de referência de reto e bexiga foram adquiridos segundo o relatório 38 do ICRU (ICRU 1985). Brevemente, o ponto de referencia retal foi determinado na radiografia latero-lateral, 5 mm atrás da parede vaginal posterior, posteriormente ao aplicador vaginal. O ponto de referencia de bexiga foi obtido utilizando-se um cateter de Foley com o balão preenchido por 7 centímetros cúbicos de fluido radiopaco. O cateter foi puxado para baixo para trazer o balão na direção da uretra. Na radiografia lateral, o ponto de referencia de bexiga foi identificado na superfície posterior da bexiga, numa linha antero-posterior identificada no centro do balão. Na radiografia antero-posterior (AP) o ponto de referência foi escolhido no centro do balão.

Seguindo as diretrizes departamentais, todos as pacientes foram tratadas com equipamento de braquiterapia de alta taxa de dose (GammaMed-Varian, Palo Alto, CA, USA), tendo como alvo os 2 centímetros proximais da cúpula vaginal. A dose foi prescrita na profundidade de 0,5 cm da superfície da mucosa. A dose total de 24 Gy (BED = 72 Gy_3/38.4 Gy_{10}) foi entregue em 4 frações de 6 Gy, cada uma espaçada por uma semana.

3.1.3 Análise da Toxicidade e desfechos oncológicos

As toxicidades agudas urinária e intestinal foram graduadas semanalmente baseando-se na escala *Common Terminology Criteria for Adverse Events* versão 4.03 (NIH-NCI 2010). As pacientes foram acompanhadas pós-tratamento com um regime de consultas ambulatoriais trimestrais nos dois primeiros anos, semestrais entre 2 e 5 anos, e anuais após 5 anos. Utilizou-se o teste t de Student para comparar as doses médias nos órgãos de risco entre o grupo das pacientes com sintomas urinários e o grupo das pacientes sem sintomas urinários. Os desfechos oncológicos foram avaliados nas pacientes com mais de um ano de seguimento. Os tempos de sobrevida foram calculados a partir da data de inicio do tratamento (data da cirurgia). Falha linfonodal pélvica isolada ou concomitante com falha local foi considerada como evento de falha pélvica. As análises de falha local e sobrevida foram realizadas pelo método de Kaplan-Meier e o teste log-rank foi utilizado para a análise de subgrupos. O comitê de ética em pesquisa aprovou este estudo.

3.2 METODOLOGIA PARTE II

3.2.1 Critérios de Elegibilidade

O estudo recrutou prospectivamente pacientes femininas com idade entre 18 e 85 anos. Os critérios de inclusão foram: diagnóstico histológico de câncer de endométrio ou colo uterino, e a realização de tomografia computadorizada de planejamento. As pacientes que não realizaram cirurgia

oncológica radical como tratamento inicial foram excluídas. O estudo foi aprovado pelo Comitê de Ética em Pesquisa em Seres Humanos da Fundação Antônio Prudente. Todas as pacientes assinaram o termo de consentimento informado antes de entrar no estudo. O protocolo foi registrado antes do inicio (NCT02091050).

3.2.2 Simulação e Tratamento

Antes da colocação do aplicador em forma de cilindro, um cateter de Foley foi inserido na uretra, para reportar a dose no ponto de bexiga ICRU (D_{ICRU}), conforme descrito no relatório 38 do ICRU (ICRU 1985), mas adaptado para imagem tomográfica volumétrica. De modo a testar a robustez dos parâmetros de dose, foram obtidas imagens de tomografia computadorizada de planejamento em dois cenários: com o cateter de Foley tensionado em direção caudal do paciente utilizando A) tensão padrão e B) tensão extra. Tensão padrão foi definida como a tensão necessária para posicionar o balão no trígono vesical. Tensão extra foi definida como uma tensão adicional limitada pelo início da sensação de desconforto da paciente. Não foi utilizado manômetro para diferenciar e quantificar com precisão os diferentes níveis de tensão. Após a inserção do aplicador vaginal, foi realizado um esforço no sentido de posicionar o cateter de modo centralizado na pelve antes da realização da tomografia de planejamento. Não foi indicada instrução especifica referente ao enchimento da bexiga.

Radiografias ortogonais simples foram obtidas antes de cada aplicação para confirmar a posição do cilindro, comparando a imagem

radiográfica simples com uma imagem radiográfica reconstruída a partir da tomografia de planejamento. A posição de litotomia foi utilizada apenas para inserção do aplicador, sendo a paciente simulada e tratada com as pernas estendidas.

Seguindo as diretrizes departamentais, todos as pacientes foram tratadas com equipamento de braquiterapia de alta taxa de dose (GammaMed-Varian, Palo Alto, CA, USA), tendo como alvo os 2 centímetros proximais da cúpula vaginal. A dose foi prescrita na profundidade de 0,5 cm da superfície da mucosa nos casos tratados com braquiterapia isolada, e na superfície nos casos tratados com braquiterapia e radioterapia externa. A dose total de 24 Gy (BED = 72 Gy_3/38.4 Gy_{10}) foi entregue em 4 frações de 6 Gy, cada uma espaçada por uma semana. A radioterapia externa pélvica foi entregue com uma dose total de 45 Gy em 25 frações de 1.8 Gy (EQD2 53.1 Gy_{10}). A dose final foi calculada adicionando a dose da radioterapia externa à dose reportada no sistema de planejamento da braquiterapia, assumindo uma distribuição homogênea da dose de 45 Gy no volume alvo de tratamento (PTV).

Os dados dosimétricos foram obtidos do sistema de planejamento (BrachyVision Eclipse® , version 11.0, Varian, Palo Alto, CA, USA), baseado na tomografia realizada antes da primeira aplicação apenas e no delineamento dos órgãos de risco descrito a seguir na metodologia da Parte III. O mesmo médico radio-oncologista delineou os órgãos de risco em todas as imagens. Os parâmetros de dose analisados na parte II foram: dose ICRU de bexiga (D_{ICRU}), ponto de dose máxima na bexiga (D_{MAX}), valor

mínimo de dose nos 0,1; 1,0; e 2,0 centímetros cúbicos de maior dose (D0.1cc, D1.0cc, D2.0cc, D4.0cc), e a dose que foi recebida por 50% da bexiga (D50%).

3.2.3 Análise estatística

A análise visual de histogramas e o teste de Shapiro-Wilk foram utilizados para definir a normalidade dos valores de distribuição de dose. O teste dos pontos sinalizados de Wilcoxcon foi utilizado para comparar as doses das variáveis de distribuição não-normal. Todas as análises estatísticas foram realizadas através do software IBM SPSS *Statistics*, versão 20.0. Armonk, NY.

3.3 METODOLOGIA PARTE III

As pacientes foram recrutadas, planejadas e tratadas conforme descrito na metodologia da Parte II.

3.3.1 Avaliação da dose

O mesmo médico radio-oncologista delineou os órgãos de risco em todas as imagens tomográficas, baseado no atlas de delineamento do *Radiation Therapy Oncology Group* (RTOG). A uretra foi delineada no trajeto do cateter de Foley, utilizando a ferramenta de delineamento de 5 milímetros, iniciando-se na parte inferior da bexiga cranialmente até o nível da tuberosidade isquiática distalmente. O trígono vesical foi definido como o

volume cônico formado pelo 1 centímetro caudal da bexiga. Os parâmetros de dose analisados foram: ponto ICRU de bexiga e reto, dose máxima em todos os órgãos de risco, dose mínima nos 0,1; 1,0; e 2,0 centímetros cúbicos de maior dose de cada órgão de risco. A única exceção foi a uretra que só teve a dose máxima e a dose mínima no 0,1 cc de maior dose analisadas devido ao reduzido volume desta estrutura.

Foi realizada tomografia de planejamento apenas antes da primeira fração, sendo as doses multiplicadas pelo número de frações (quatro), baseado num estudo da Universidade de Emory (CORSO et al. 2013), no qual os pesquisadores demonstraram que, especificamente para braquiterapia de fundo vaginal, não há diferença estatisticamente significante na dose reportada nos parâmetros entre os protocolos de imagem apenas na primeira fração versus imagem antes de cada aplicação.

3.3.2 Avaliação da Toxicidade

As toxicidades agudas urinária e intestinal foram graduadas semanalmente baseando-se na escala *Common Terminology Criteria for Adverse Events* versão 4.03 (NIH-NCI 2010) durante o tratamento (com avaliação ambulatória semanal) e nas consultas de seguimento até 3 meses após o término do tratamento.

3.3.3 Desfechos e Análise estatística

Inicialmente, histogramas de dose-toxicidade foram analisados visualmente para determinar possíveis valores de corte de dose para incidência de eventos adversos, os quais foram utilizados para categorizar os parâmetros de dose. Em seguida, a hipótese nula de que as duas categorias criadas foram iguais em termos de toxicidade foi testada. Os desfechos de toxicidade utilizados foram: eventos de toxicidade intestinal grau 2 ou maior e eventos de toxicidade urinaria grau 1 ou maior.

Adicionalmente, os seguintes fatores relacionados as pacientes e ao tratamento foram relacionados com o risco de toxicidade utilizando-se o teste exato de Fisher: tumor primário (endométrio ou colo uterino), utilização de quimioterapia concomitante, e irradiação para-aórtica. Todas as análises estatísticas foram realizadas utilizando o programa IBM SPSS Statistics, versão 20.0. (Armonk, NY).

4 ARTIGO

4.1 PARTE I - JOURNAL OF CONTEMPORARY BRACHYTHERAPY

Clinical Investigations

Original paper

Bladder (ICRU) dose point does not predict urinary acute toxicity in adjuvant isolated vaginal vault high-dose-rate brachytherapy for intermediate-risk endometrial cancer

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Abstract

Purpose: High-dose-rate brachytherapy (HDR-BT) alone is an adjuvant treatment option for stage I intermediate-risk endometrial cancer after complete surgical resection. The aim of this study was to determine the value of the dose reported to ICRU bladder point in predicting acute urinary toxicity. Oncologic results are also presented.

Material and methods: One hundred twenty-six patients were treated with postoperative HDR-BT 24 Gy (4 × 6 Gy) per ICRU guidelines for dose reporting. Cox analysis was used to identify variables that affected local control. The mean bladder point dose was examined for its ability to predict acute urinary toxicity.

Results: Two patients (1.6%) developed grade 1 gastrointestinal toxicity and 12 patients (9.5%) developed grades 1-2 urinary toxicity. No grade 3 or greater toxicity was observed. The mean bladder point dose was 46.9% (11.256 Gy) and 49.8% (11.952 Gy) for the asymptomatic and symptomatic groups, respectively ($p = 0.69$). After a median follow-up of 36.8 months, the 3-year local failure and 5-year cancer-specific and overall survival rates were 2.1%, 100%, and 94.6%, respectively. No pelvic failure was seen in this cohort. Age over 60 years ($p = 0.48$), lymphatic invasion ($p = 0.77$), FIGO histological grade ($p = 0.76$), isthmus invasion ($p = 0.68$), and applicator type (cylinder × ovoid) ($p = 0.82$) did not significantly affect local control.

Conclusions: In this retrospective study, ICRU bladder point did not correlate with urinary toxicity. Four fractions of 6 Gy HDR-BT effected satisfactory local control, with acceptable urinary and gastrointestinal toxicity.

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Key words: endometrial cancer, high-dose-rate brachytherapy, ICRU 38, urinary toxicity.

Purpose

Radiotherapy is an important adjuvant treatment option for intermediate-risk stage I endometrial cancer. Several phase III trials have shown that radiotherapy in intermediate-risk patients decreases locoregional recurrences but does not improve survival [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. Regarding vaginal control, the Postoperative Radiation Therapy in Endometrial Cancer (PORTEC-2) trial concluded that isolated brachytherapy (BT) is equivalent to external beam radiotherapy (EBRT) for intermediate-risk patients [8]. Moreover, BT is associated with less gastrointestinal toxicity [2, 8, 11].

Report number 38 by the International Commission on Radiation Units and Measurements (ICRU) established the technical basis for 2-dimensional intracavitary BT [12], and suggested that the dose to the bladder and rectum be reported using reference points, visualized on simple orthogonal X-rays. Recently, regarding vaginal vault treatment, the American Brachytherapy Society (ABS) also recommended considering the documentation of doses to the adjacent normal tissue, particularly of these 2 adjacent organs at risk (OARs) [13].

In low-dose-rate (LDR) BT, for example, Perez *et al.* demonstrated a lack of correlation between rectal point dose and the incidence of late grade 2 rectosigmoid toxicity, and between ICRU bladder point dose and grade 2 or 3 urinary toxicity [14]. No study has examined the clinical significance of ICRU points and their ability to predict toxicity in treatment with high-dose-rate (HDR) BT alone.

The main objective of this study was to report toxicity to the rectum and bladder, and evaluate the reliability of

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the dose to the bladder in predicting urinary toxicity with postoperative vaginal vault HDR-BT alone. Further, we analyzed local failure (LF), pelvic failure (PF), metastasis incidence (MI), and overall survival (OS) in a cohort of patients who were treated with BT for intermediate-risk stage I endometrial cancer.

Material and methods

Eligibility criteria

The study cohort comprised patients with endometrial cancer who were initially treated with complete surgical resection and staging; classified as having stage I, intermediate-risk disease, and subsequently treated between 2009 and 2013. This period was selected to avoid the need for pelvic external beam irradiation for intermediate-risk stage I endometrial cancer, because our institutional guidelines changed after publication of the PORTEC-2 study [8].

The intermediate-risk patients were divided in 2 subgroups. The high-intermediate-risk (HIR) group was based on the PORTEC-2 eligibility criteria: age greater than 60 years and 2009 FIGO stage IB (invasion greater than 50% of the myometrium) with grade 1 or 2 disease or 2009 FIGO stage IA (invasion less or equal 50% of the myometrium) with grade 3, and stage IIA disease, any age (except grade 3 with greater than 50% myometrium invasion). The remaining patients were classified as low-intermediate-risk (LIR), excluding low-risk IA G1 (without adverse pathological findings, such as lymphatic invasion and isthmus involvement).

Dosimetry

Dosimetric data were obtained from the treatment planning system (Eclipse®, version 11.0, Varian, Palo Alto, CA, USA) using simple orthogonal X-ray images (Figure 1). Reference points for rectal and bladder doses were acquired per ICRU 38 guidelines [12]. Briefly, the point of reference for the rectal dose was determined in the lateral radiograph, 5 mm behind the posterior vaginal wall, posterior to the vaginal applicator. The bladder reference point was obtained using a Foley catheter with the balloon filled with 7 cc of radio-opaque fluid. The catheter was pulled downward to bring the balloon against the urethra. On the lateral radiograph, the bladder reference point was identified on the posterior surface of the balloon, on an anterior-posterior line through the center of the balloon. On the anterior-posterior (AP) radiograph, the reference point was taken as the center of the balloon.

Per institutional protocols, all patients were treated with HDR-BT devices (GammaMed-Varian, Palo Alto, CA, USA), targeting the proximal 2 cm of the vaginal vault for vaginal cylinders or the vaginal vault for ovoids. Although we did not report such values, the 2 cm-proximal vaginal target was intended to decrease the vaginal late toxicity rate. The dose was prescribed at a depth of 0.5 cm

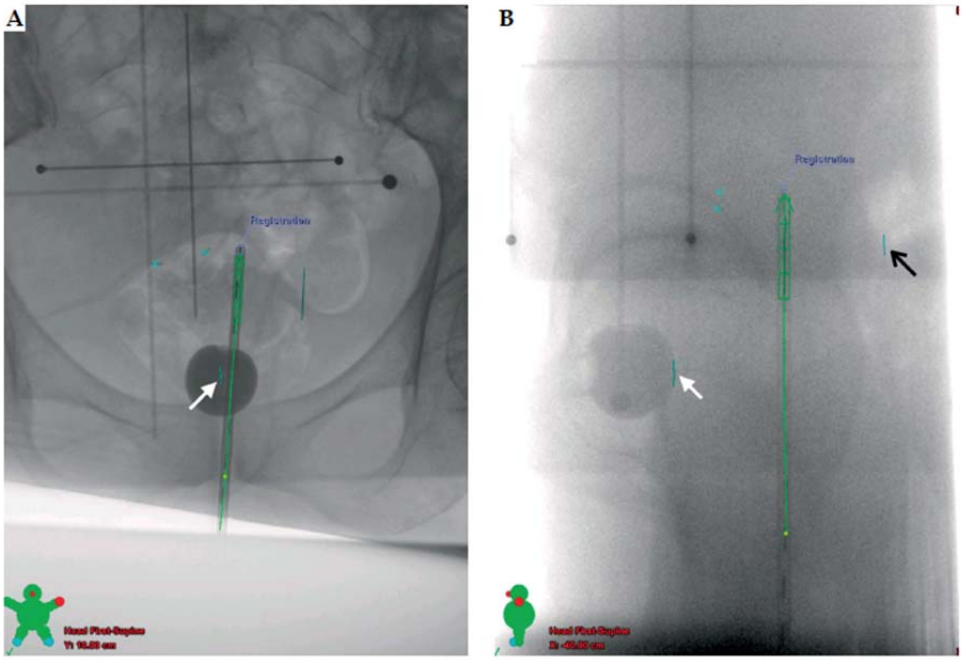

Fig. 1. Example of simple orthogonal X-ray images used for localization of vaginal cylinder and ICRU bladder (white arrow) and ICRU rectal reference points (black arrow) per the ICRU 38 report. A) Anteroposterior projection. B) Lateral projection

from the mucosal surface. The dose was 24 Gy, delivered in 4 weekly fractions of 6 Gy (BED = 72 Gy_3/38.4 Gy_{10}). This regimen had an EQD_2 dose of 32 Gy (α/β ratio = 10).

Toxicity scoring

Acute toxicity was graded per the Common Terminology Criteria for Adverse Events (CTCAE v4.0) [15], and all patients were followed weekly during the treatment to assess acute toxicities. This study was limited to the evaluation of urinary and rectal toxicity. By student's *t*-test, we compared the mean doses of OARs between groups with (symptomatic group [SG]) and without urinary toxicity (asymptomatic group [AG]).

Treatment outcomes

Treatment outcomes were evaluated for patients with more than 1 year of follow-up. Survival times were calculated from the date of initiation of therapy (date of surgery). Pelvic lymph node recurrence alone or concurrent with local failure was considered PF. Local failure and survival analyses were performed by Kaplan-Meier method and log-rank test was used for the subgroup analysis. The institutional ethics research committee approved this study.

Results

One hundred twenty-six consecutive patients were analyzed. The median age at diagnosis was 61 years (range: 29-86). Seven patients were excluded from the analysis of oncological outcomes, because they were retrospectively considered to be high-risk (n = 6) or low-risk without adverse pathological findings (n = 1) but were included in the toxicity analysis. The median tumor size was 3.1 cm (range: 0.6-9.6 cm). The patients and treatment profiles are detailed in Table 1. Brachytherapy treatments were delivered with a cylinder (94.4%) or ovoids (5.6%) at the discretion of the physician.

Two patients (1.6%) developed grade 1 gastrointestinal (GI) toxicity and 12 patients (9.5%) developed grades 1-2 urinary (GU) toxicity (Table 2). No grade 3 or greater GI or GU toxicity was observed. The mean bladder point dose was 46.9% of prescription (11.26 Gy) for the AG, and 49.8% of prescription (11.95 Gy) for the SG (p = 0.69). Of the 7 patients with grade 2 urinary toxicities, three (42.8%) were also diagnosed with urinary tract infection, requiring treatment with oral antibiotics. As expected, the dose at the ICRU rectal point was 24 Gy in all cases, because the reference line for prescription (0.5 cm depth from the mucosal surface) included the rectal reference point.

For patients with more than 1 year of follow-up (n = 104), after a median of 36.8 months, there were 2 vaginal failures (both at 18 months of follow-up) and 2 deaths, none that was related to progression of endometrial cancer (1 case of acute myocardial infarction and 1 case of sepsis after an attempt at surgical removal of an intestinal adhesion). The 3-year LF rate was 2.1% (Figure 2A). The 5-year cancer-specific survival rate was 100%. As shown in Figure 2B, the 5-year OS was 94.6%. No pelvic failure was observed in this cohort. One patient developed distant metastasis to the lungs after 24 months of follow-up but remains alive after 1 year.

In a subgroup analysis, although both failures occurred in patients aged older than 60 years, age was not a statistically significant predictor of LF (p = 0.48) (Figure 2C). The IHR group was not associated with an increased risk of LF compared with intermediate-low-risk patients (p = 0.91) (Figure 2D). Similarly, lymphatic invasion (p = 0.77), FIGO histological grade (p = 0.76), isthmus invasion (p = 0.68), and applicator type (cylinder vs. ovoid) (p = 0.82) were not linked to LF (Figure 2C,D). Also,

Table 1. Patients and treatment characteristics

Factors	*N*	%
Age		
< 60 y	54	42.9
> 60 y	72	57.1
Lymphadenectomy		
None	18	14.3
Sampling*	14	11.1
Systematic**	79	62.7
Not available	15	11.9
FIGO group		
IAG1	7	5.6
IAG2	46	36.5
IAG3	34	27
IBG1	14	11.1
IBG2	21	16.7
IBG3	3	2.4
IIAG2	1	0.8
Isthmus involvement		
Negative	107	84.9
Positive	19	15.1
Angiolimphatic invasion		
Negative	118	93.7
Positive	8	6.3

**Sampling: less than 12 lymph nodes removed. **Systematic: 12 or more lymph nodes removed. FIGO 2009 staging*

Table 2. Toxicity

Grade	GI (*n*, %)	GU (*n*, %)	Positive urine culture (*n*)	Positive urine culture (%)
1	2 (1.6)	5 (4)	0	0
2	0	7 (5.5)	3	42.8
3-5	0	0	0	0

GI – gastro-intestinal, GU – genito-urinary

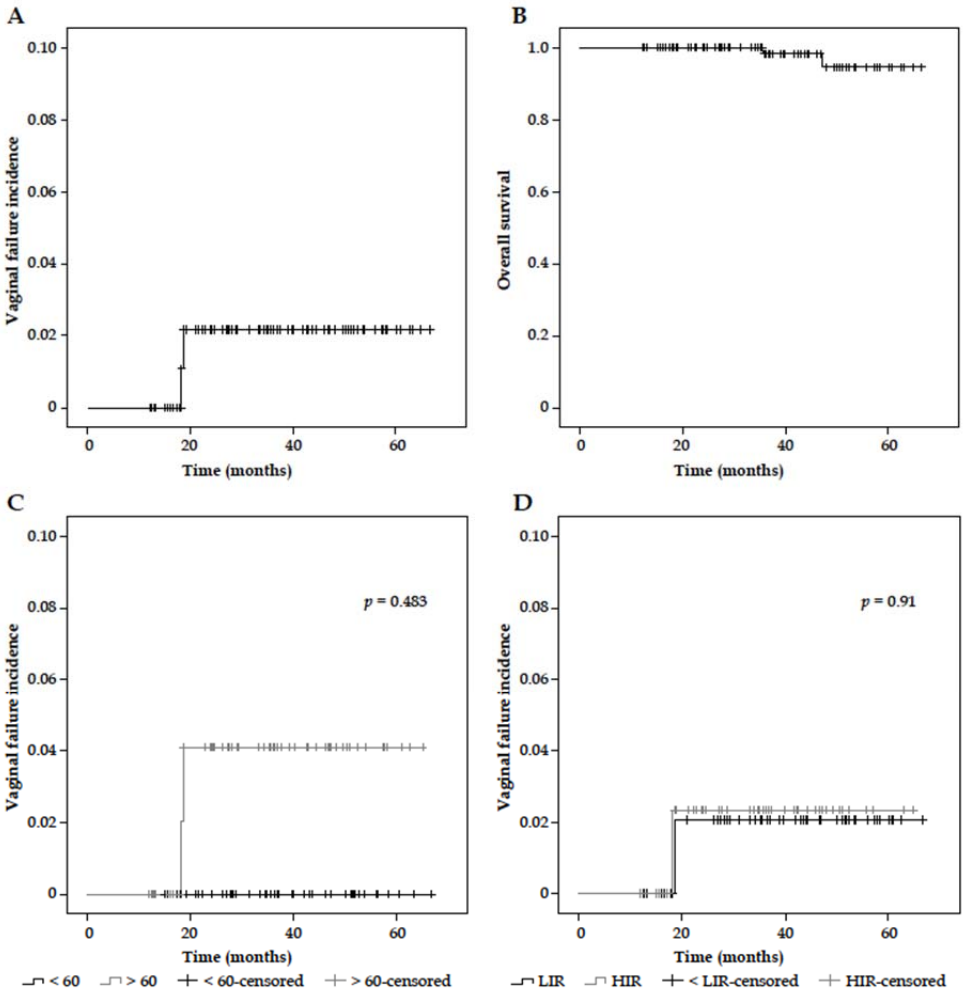

Fig. 2. Kaplan-Meier survival tables. A) Incidence of vaginal failure. B) Overall survival. C) Incidence of vaginal failure as a function of age. D) Incidence of vaginal failure as a function of risk. LIR – low-intermediate-risk; HIR – high-intermediate-risk

lymphadenectomy failed to correlate with differences in local recurrence ($p = 0.43$) and OS – the 5-year OS rates were 95.5% and 94.7% with and without lymphadenectomy, respectively ($p = 0.44$).

Discussion

The small number of events [3 disease failures (2 LF and 1 distant metastasis) and 14 treatment G1-G2-related adverse effects] in this cohort demonstrates the outstanding prognosis and safety profile of using BT alone in the adjuvant treatment of stage I intermediate-risk endometrial cancer patients.

In this study, 1.6% of patients developed acute G1-G2 GI toxicity, which is favorable compared with the vaginal brachytherapy-alone arm in PORTEC-2 [8], which reported a 12.6% acute GI-G2 GI toxicity rate. This excellent toxicity profile, even with the higher EQD_2 dose in our regimen – 32 Gy vs. 29.8 Gy in PORTEC-2 – can be explained in part by the activation of sources at only 2 cm of the vaginal vault. Because our study did not evaluate vaginal toxicity, and because PORTEC-2 did not present acute GU toxicity, these adverse effects were not compared.

ICRU classically establishes surrogate points for the assessment of toxicity, based on 2-dimensional references [12]. The principal criticism of these points is the lack

of a proven correlation between the reference point for calculation of the dose and clinical toxicity. This finding might be due to technical inaccuracies in the dose measurements, considering that these points are bidimensional representations of a 3-dimensional distribution of dose. There are differences between the ICRU bladder dose and the volumetric (0.1 cc, 1 cc, and 2 cc) or maximum dose to this organ [16]. Also, the recommendation by the ICRU to pull down the catheter to place the balloon against the urethra is one example of a potential source of inaccuracy [12]. The pressure that is used can generate variable displacement of the reference point, because this is related to the position of the balloon, which might fail to be accompanied by equal displacement of the bladder.

In addition to the technical uncertainties of vaginal cuff brachytherapy alone, the exact origin of acute symptoms is unknown. The urinary pain that is associated with therapeutic radiation might be related to the dose to the entire bladder, part of the organ, trigone of bladder [17], and the urethra [18]. As noted in our study, the urine analysis diagnosed an infection in over 40% of cases with grade 2 urinary toxicity, likely due to bladder catheterization, a possible explanation for urinary pain. This finding suggests another limitation of the ICRU dose reporting system, which requires the presence of the urinary catheter balloon inside of the bladder to estimate its position [12]. Similarly, there might be a causative relationship between the dose to the rectum, sigmoid [19], individual loops of the small bowel, and the intestinal bag and gastrointestinal symptoms but the limited number of gastrointestinal toxicity events made it impossible to draw any conclusions about the value of the ICRU rectal point.

Conversely, planning with computed tomography-assisted brachytherapy can guide individualized treatment of the vagina with better coverage of any tissue behind the mucosa that is inaccessible by physical examination or simple x-ray, and predict the dose to OARs, possibly improving the toxicity profile [20, 21]. Although the dosimetric differences between ICRU point data and the maximum doses by volumetric analysis using ultrasonography [22] or computerized tomography [23] are known, no study has demonstrated the superiority of these image methods over the evaluation of simple orthogonal x-ray reference points. To this end, a recently opened trial (NCT 02091050) is recruiting patients who have undergone hysterectomy for gynecological neoplasms to compare the accuracy of 2D vs. 3D planning with regard to the ability to predict toxicity.

All patients were homogeneously treated with adjuvant brachytherapy, and although lymphadenectomy was performed at the discretion of the surgeon, 60% of subjects underwent systematic pelvic lymphadenectomy. However, the extent of lymph node resection did not influence their outcomes, as suggested by the results of other more powered studies [24, 25]. This rate of lymphadenectomy, in turn, is more favorable than the PORTEC-2 trial [8], in which the incidence of pelvic failure was 3.8% in patients who did not undergo lymph node resection and were randomized to the no-pelvic radiation treatment arm.

Regarding the oncological results, our study is one of the largest experiences with HDR BT, using a fractionation of 4 × 6 Gy, and demonstrating equivalent results with over 97% vaginal control in 3 years, as the PORTEC-2 trial [8]. Excellent local control for low-risk endometrial cancer was achieved by Petereit *et al.* [26], using 2 insertions of 16.2 Gy each, prescribed to the vaginal surface. Similar results have been published, with over 95% vaginal vault local control in intermediate-risk cases using 5 fractions of 5.5 Gy [27] and 3 fractions of 7 Gy [28, 29]. Because most local recurrences occur during the first 2 years of follow-up, our median follow-up time of 37 months appears to be adequate for evaluating local recurrences in this retrospective cohort.

Conclusions

A favorable toxicity profile (less than 10% grade 1-2 acute reactions) could not be predicted by the ICRU 38 urinary reference point. The reliability of the ICRU 38 urinary reference point in this setting should be reevaluated in future trials. HDR BT alone with 4 fractions of 6 Gy is an adequate fractionation schedule for adjuvant treatment of intermediate-risk (high or low) stage I endometrial cancer in terms of local control.

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Disclosure

Authors report no conflict of interest.

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4.2 PARTE II – SCIENTIFIC REPORTS

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Volumetric (3D) bladder dose parameters are more reproducible than point (2D) dose parameters in vaginal vault high-dose-rate brachytherapy

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There is no consensus on the use of computed tomography in vaginal cuff brachytherapy (VCB) planning. The purpose of this study was to prospectively determine the reproducibility of point bladder dose parameters (D_{ICRU} and maximum dose), compared with volumetric-based parameters. Twenty-two patients who were treated with high-dose-rate (HDR) VCB underwent simulation by computed tomography (CT-scan) with a Foley catheter at standard tension (position A) and extra tension (position B). CT-scan determined the bladder ICRU dose point in both positions and compared the displacement and recorded dose. Volumetric parameters (D0.1cc, D1.0cc, D2.0cc, D4.0cc and D50%) and point dose parameters were compared. The average spatial shift in ICRU dose point in the vertical, longitudinal and lateral directions was 2.91 mm (range: 0.10–9.00), 12.04 mm (range: 4.50–24.50) and 2.65 mm (range: 0.60–8.80), respectively. The D_{ICRU} ratio for positions A and B was 1.64 ($p < 0.001$). Moreover, a decrease in Dmax was observed ($p = 0.016$). Tension level of the urinary catheter did not affect the volumetric parameters. Our data suggest that point parameters (D_{ICRU} and Dmax) are not reproducible and are not the ideal choice for dose reporting.

Postoperative vaginal cuff brachytherapy (VCB) with or without external beam radiation therapy (EBRT) is an integral component of the adjuvant treatment of endometrial cancer[1], and this combination is an option in certain cases of cervical cancer[2].

The documentation of the dose to organs at risk (OARs) during gynecological intra-cavitary brachytherapy was formally stated by the International Commission on Radiation Units and Measurements (ICRU) in 1985[3]. Published in 2006[4], the Groupe Européen de Curiethérapie (GEC) and the European Society for Radiotherapy and Oncology (ESTRO) recommendations for 3D image-based brachytherapy, directed to cervical cancer, advocate documentation of the dose to the bladder with the ICRU reference point and D0.1cc, D1.0cc and D2.0cc (volumetric parameters). In 2012, the American Brachytherapy Society (ABS) published a consensus guideline on recommendations for VCB[5], including reporting the dose to adjacent organs, particularly the bladder and rectum, but did not specify the exact parameters.

Currently, the choice between point dose parameters, such as ICRU bladder point dose (D_{ICRU}) and maximum bladder dose (Dmax), and volumetric parameters relies solely on dosimetric evidence[6–12]. Several studies have compared ICRU and volumetric dose, but the lack of a relation or difference between them prevents either from being recommended over the other. Thus, evidence of the superiority of 3D planning in terms of predicting toxicity over 2D planning—or a technical limitation of the 2D planning—must be provided to justify the use of volumetric parameters in the post-hysterectomy setting.

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With standard tension		With extra tension	
D_{ICRU} × Dmax	**p < 0.001**	D_{ICRU} × Dmax	**p < 0.001**
D_{ICRU} × D0.1cc	**p < 0.001**	D_{ICRU} × D0.1cc	**p < 0.001**
D_{ICRU} × D1.0cc	**p = 0.001**	D_{ICRU} × D1.0cc	**p < 0.001**
D_{ICRU} × D2.0cc	**p = 0.003**	D_{ICRU} × D2.0cc	**p < 0.001**
D_{ICRU} × D4.0cc	**p = 0.020**	D_{ICRU} × D4.0cc	**p < 0.001**
D_{ICRU} × D50%	**p < 0.001**	D_{ICRU} × D50%	**p < 0.001**

Table 1. Comparison between ICRU bladder dose point and other bladder dose parameters.

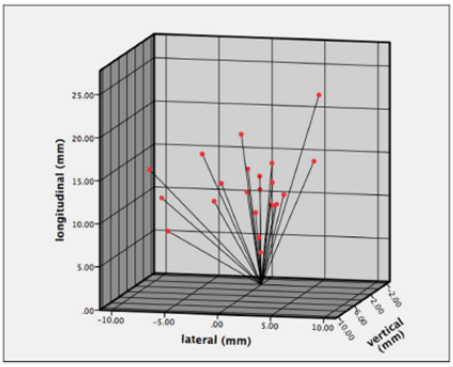

Figure 1. 3D scatterplot of catheter spatial displacement between positions A and B.

Our aim was to prospectively demonstrate the limitations in reproducing conventional point-based dosimetry after comparing bladder volumetric dose parameters with bladder point dose parameters in the treatment of vaginal apex treatment, using two different tension levels for positioning of the Foley catheter.

Results

Twenty-two patients were prospectively enrolled in this study between June 2014 and February 2015, totaling 44 CT scans (22 in position A and 22 in position B). Seventeen subjects had endometrial cancer (11 stage I, 1 stage II, 5 stage III), and 5 had cervical cancer (4 stage I and 1 stage II). Fifteen patients received EBRT + BT (53% tri-dimensional conformal radiation therapy and 47% intensity-modulated radiation therapy), and 7 received BT alone. The diameter of the cylinder was 26 mm in 36.4% of patients and 30 mm in 63.6%, according to patient anatomy. Two patients received para-aortic irradiation. There were no complications that were related to insertion of the Foley catheter at the time of the CT scan. The patients were treated with the catheter in standard position.

Data from all 44 treatment plans were available for analysis. None of the parameters (in terms of average doses) was normally distributed.

Comparison between point dosimetry and volumetric dosimetry. Based on a normalized dose value (based on the percentage of the prescribed dose), the average D_{ICRU} documented in position A was 2.68 Gy, comprising 44.6% of the total prescribed dose.

Compared with standard tension, the bladder D_{ICRU} value differed significantly from Dmax ($p < 0.0001$), with a Dmax/D_{ICRU} ratio of 2.32. The same results were seen with the volumetric parameters and in comparison with position B (Table 1).

Impact of Foley catheter tension on dose parameters. Considering position A as the reference, significant displacement of the balloon center to position B was observed in the longitudinal direction. The average shift in the vertical, longitudinal and lateral directions was 2.91 mm (range: 0.10–9.00), 12.04 mm (range: 4.50–24.50) and 2.65 mm (range: 0.60–8.80), respectively. Figure 1 shows the spatial displacement in each patient, based on position A, which is defined as (0, 0, 0) in the 3D graph.

With respect to reproducibility, the average D_{ICRU} was 2.68 Gy (44.6%) in position A and 1.63 Gy (27.1%) in position B ($p < 0.001$). The D_{ICRU} ratio between positions A and B was 1.64. A significant decrease in maximum dose ($p = 0.016$) was also observed. For the other parameters, the position A/B ratio was 1.023 (D0.1cc), 1.006 (D1.0cc), 1.005 (D2.0cc), 1.032 (D4,0cc) and 1.027 (D50%). The percentage change in each parameter is listed in Table 2.

Parameters	Foley catheter tension (normalized*)		% change	*p* value
	Standard tension	Extra tension		
D_{ICRU}	44.6	27.1	39.2	**p < 0.001**
Dmax	103.5	98.3	5.0	**p = 0.016**
D0.1cc	88.1	86.1	2.3	p = 0.123
D1.0cc	72.3	71.8	0.7	p = 0.390
D2.0cc	65.3	65	0.5	p = 0.372
D4.0cc	57.1	57	0.2	p = 0.269
D50%	12.3	12	2.4	**p = 0.002**

Table 2. Summary of statistics by parameter and tension applied to Foley catheter. *Normalized as percentage of prescribed dose. SD = standard deviation. D_{ICRU} = dose reported using ICRU bladder point visualized in CT plan.

Discussion

This study is the first controlled analysis that addresses the limitations of bladder point dosimetric data, in terms of reproducibility. Earlier reports on vaginal vault treatment have merely evaluated the differences between the averages values of ICRU bladder point dose and volumetric parameters; thus, this drawback of point dosimetry argues in favor of 3D planning.

Although the use of CT scan for dose calculation in VCB is attractive, no study has proven the superiority of volumetric data against classical ICRU points with regard to predicting urinary toxicity, necessitating a discussion of the cost-effectiveness of planning with tridimensional imaging in VCB compared with simple x-ray due to the minimal optimization of the applicators[13–15], lack of clinical correspondence of the reported dose[16] and significant rise in procedure costs[7].

The ICRU 38 states that "the catheter is pulled downwards to bring the balloon against the urethra"[3]. This orientation is fundamental to the localization of the ICRU bladder point, since this document claims that "on the lateral radiograph, the reference point is obtained on an anterior-posterior line drawn through the center of the balloon. The reference point is taken on this line at the posterior surface of the balloon. On the frontal radiograph, the reference point is taken at the center of the balloon". In this setting, due to the possible variation between different physicians, or even between different insertions performed by the same physician, our study evaluated the impact of various levels of tension (A-standard vs B-extra tension) on catheter spatial position and dose reported to the bladder.

The documented spatial change in the catheter exceeded 10 mm in 1 or more directions in 68% of the patients, translating into an overall reduction in the ICRU bladder point dose of 39% (44.6% to 27.1% of the prescribed dose) and confirming our hypothesis that an intrinsic limitation of the ICRU bladder point dosimetry in terms of reproducibility can lead to a bias. Additionally, Dmax, another point dose analysis, was also significantly affected by catheter position but to a lower extent (5% absolute reduction). Notably, the volume-based parameters were not influenced, with the exception of D50%. These findings could be explained by the hypothesis that the different tension level applied altered the ballon position (changing the ICRU measurement) but not the bladder anatomic position (determined by the constant volumetric doses) in relation to the high-dose region.

Two studies compared D_{ICRU} versus volumetric bladder dose that was reported by computed tomography planning using a single-lumen vaginal cylinder in the vaginal apex. Russo *et al.*[6] published a retrospective dosimetric study, analyzing the Dmax and D2cc of the first 20 patients who were treated with CT-based 3D planning after a departmental policy change toward this method. They compared the doses to ICRU bladder point that was recorded from 71 patients who had been previously treated in the same institution, based on plain-film orthogonal radiographs. The average normalized bladder dose (as percentage of prescribed dose) was significantly higher with Dmax (x1.78) but not D2cc (x1.08), compared with D_{ICRU}. These differences might be attributed to the lack of 2D and 3D information being collected from the same patients.

In the second study, Hung *et al.*[8] prospectively examined the dosimetric effects of bladder filling on OARs and noted a reduction in D2cc values for the small bowel but not the bladder. As expected, the D50% (dose received by 50% of bladder volume) was significantly reduced with a full bladder, due to the increase in volume. Using a similar method as ours, after simulation of the ICRU point position on CT images, they recorded a mean D2cc/D_{ICRU} ratio of 0.95. The difference in mean D_{ICRU} between an empty and full bladder was 16 cGy and corresponded to an increase of 1.3% increase with an empty bladder (*p*-value not provided). These findings suggest the reproducibility of the ICRU point regarding bladder filling. Table 3 compares the characteristics of these studies.

In our series, the same physician delineated the OARs to limit the discrepancies in contouring between assistants. One possible limitation of our study was the absence of a CT scan in every insertion, because possible changes in bladder[8–10] or rectal[11] filling might have influenced the reported dose to the OARs. Moreover, Hoskin *et al.*[17] documented that the angulation of the cylinder can also alter the dose in the bladder and rectum. It's reasonable to hypothesize that the extra-tension could act as another source of displacement of vaginal vault, which was not controlled in our analysis, but should be tested in future studies. However, other studies suggest that the evaluation of the first insertion is sufficient in terms of dose reporting[9,18]; this is the current approach at our institution. Another limitation is the absence of a documented manometer reading, which can measure various levels of tension and help reproduce the findings of our study. The normalization that was performed by Russo *et al.*[6], based on the prescribed dose as the denominator, is recommended for studies that compare different dose

Study	Year	n	Design	CT planning	Ratio Dmax/D_{ICRU}	Ratio D2cc/D_{ICRU}
Russo *et al.*[6]	2012	71 (2D) 20 (3D)	retrospective	every fraction	1.79	1.08
Hung *et al.*[8]	2012	12 (2D and 3D) empty bladder	prospective	1st fraction only	NR	0.92
		12 (2D and 3D) full bladder			NR	0.98
present study	2015	22 (2D and 3D) standard tension	prospective	1st fraction only	2.32	1.46
		22 (2D and 3D) extra tension			3.62	2.39

Table 3. Design of published studies that have compared bladder D_{ICRU} and other parameters in VCB.

parameters and is essential for studies that use different doses per fraction, to make the results between studies comparable. In our data, the normalization was meant to account for differences in the prescription reference line, because patients who received VCB alone had 6 Gy/fraction prescribed to 0.5 cm from the cylinder surface, and those who received both VCB and EBRT were targeted at the surface.

Our group recently published a retrospective series on 126 patients who were treated with high-dose-rate VCB alone for intermediate-risk endometrial cancer with a 9.5% rate of grades 1 or 2 acute urinary toxicity and no case of grade 3 toxicity[16]. We did not find any differences in bladder ICRU point doses between the asymptomatic group and symptomatic group, with 11.256 Gy × 11.952 Gy ($p = 0.69$), respectively. Additionally, the use of a Foley catheter was deemed to be responsible for part of the acute toxicity reported, due to an inherent increased risk of urinary tract infection[7,16]. Despite the low rates of grades 3 and 4 urinary toxicity in the literature after VCB alone (<3%)[5], the combination with EBRT could lead to serious complications, like bowel perforation and urethral strictures[1]. Additionally, the documentation of the previous treatment dose to OARs can more accurately define an opportunity for re-irradiation, in cases of recurrence.

Nevertheless, contrasting results have been reported by studies that have addressed the dosimetric difference of point versus dosimetric parameters in high-dose-rate brachytherapy for radical treatment of cervical cancer (intact uterus). Some studies suggest a tendency in the correlation[19,20], whereas others do not[21]. Although our findings support the adoption of CT-based planning in VCB, its generalization to HDR in the intact uterus should be supported by specific studies.

Further, additional studies are necessary to identify better predictors of toxicity in HDR brachytherapy for the vaginal vault and for radical treatment of cervical cancer and inoperable endometrial cancer. In these settings, our findings might support future trial designs that include 3D planning. It might be better to define the extension or particular anatomy of the vaginal vault and superior vaginal mucosa, leading to changes in the prescription method to volumetric instead of merely using a reference from the applicator surface or target surrogates.

In conclusion, the dose reported to the bladder using bladder D_{ICRU} or Dmax is dependent on the tension of the balloon in VCB. Because volumetric parameters (D0.1cc, D1.0cc and D2.0cc) are independent of the anatomical changes due to the presence of a urinary catheter, they might be a better option. Further analysis of toxicity outcomes is needed to determine the most appropriate dose parameter.

Methods

Patients. The study recruited female patients aged between 18 and 85 years. The inclusion criteria were a histological diagnosis of cervical or endometrial cancer and a computed tomography scan (CT scan) that was available in the planning system. Patients who did not undergo oncological surgery as the initial treatment were excluded. The institutional review board, named *Comitê de Ética em Pesquisa em Seres Humanos da Fundação Antônio Prudente*, approved this study design and the use of patient information without name or facial identification. All patients signed informed consent forms before study entry. The protocol was registered earlier (NCT02091050), and the methods were carried out in accordance with the approved guidelines.

Simulation and Insertions. Before insertion of the applicator, a Foley catheter was inserted into the urethra, to report the ICRU bladder dose (D_{ICRU}), as described in the ICRU 38 report[3], but adapted to the computed tomographic image. Briefly, on the sagittal view of the tomographic image, the bladder reference point was obtained on the posterior surface of the balloon, on an anterior-posterior line through the center of the balloon. On the coronal view, the reference point was defined as the center of the balloon, mimicking the position in the traditional simple x-ray image (Fig. 2a).

To test the robustness of the dose parameters, CT scan images were obtained in two scenarios: with the Foley catheter tensioned towards the caudal direction of the patient using standard tension and extra tension (Fig. 2b). Standard tension (position A) was defined as the tension that was necessary to position the balloon at the bladder trigone. Extra tension (position B) was defined as additional tension in the catheter, limited by the patient's complaint of discomfort. The CT scan had the following characteristics: voltage 120 kV, current 275 mA and exposure 300 mAs. A manometer was not used to identify different tension levels. After insertion of the vaginal applicator, limited effort was made to correct the insertion angle to a central position in the pelvis before performing the CT-scan. It was not provided a specific instruction concerning bladder filling. Because the two images were taken in a short interval (less than 2 minutes), the volume of the bladder was considered to be constant between positions A and B (average 350.560.4 mL and 360.4 mL, respectively).

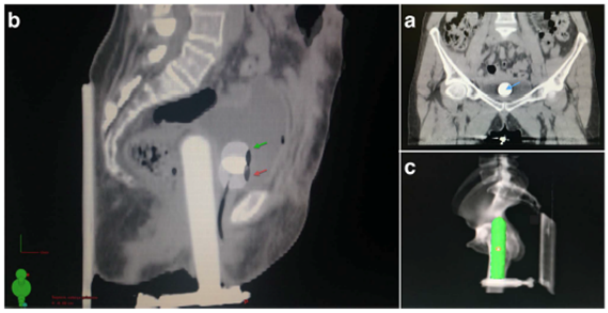

Figure 2. (a) Sagittal view of the fused planning CT scan at both tension levels: standard (position A, green arrow) and extra tension (position B, red arrow). (b) Bladder reference point identified at the center of the balloon on a coronal plane (blue arrow). (c) Digitally reconstructed radiograph (DRR) from the CT scan in position A.

Lateral and anteroposterior simple x-ray images were taken before each subsequent insertion to confirm the position of the cylinder, comparing the radiographic image with a digitally reconstructed radiograph (DRR) from the CT-scan in position A (Fig. 2c). Again, limited effort was made to correct the insertion angle, with posterior documentation of the final position with the other set of x-ray images. The lithotomy position was used only during insertion of the applicator, and the patients underwent the simulation and treatment with their legs extended.

Prescription and Dosimetry. The total dose was 24 Gy, delivered in 4 weekly fractions of 6 Gy (EQD2 38.4 Gy) to the cylinder surface in EBRT + VCB cases and 0.5 cm from the applicator surface in cases that were treated with VCB alone, to cover more of the mucosa. Because no patient presented with vaginal extension of the tumor, based on the pathological report, the cylinder was activated only at the proximal 2 cm, at the department's discretion.

The brachytherapy planning and dosimetric data were obtained from the treatment planning system (BrachyVision Eclipse®, version 11.0, Varian, Palo Alto, CA, USA), based on the CT-scan that was performed before the first procedure. The same physician contoured the OARs in all images. The dose parameters analyzed were: bladder reference point (D_{ICRU}); maximum bladder point (Dmax bladder); the minimum dose value in the 0.1 cc, 1.0 cc, 2.0 cc and 4.0 cc receiving the highest dose (D0.1cc, D1.0cc, D2.0cc, D4.0cc) and the dose that was received by 50% of the bladder (D50%).

The treatment was delivered using a GammaMedplus™ iX high-dose-rate device (VARIAN, Palo Alto, CA, USA), using the AAPM TG-43 formalism. The ^{192}Ir Gammamed HDR plus source listed in the library of origin was used.

Statistical analysis. Visual observation of the histograms and Shapiro-Wilk's test[22] ($p > 0.05$) were used to define the normality of the distribution of doses. Wilcoxon signed rank test[23] was used to compare doses of non-normally distributed dependent variables. All statistical analyses were performed using IBM SPSS Statistics, version 20.0. Armonk, NY.

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Author Contributions

L.G.S., R.C. and G.B. conceived of and designed the study. L.G.S., A.F. and A.A. performed the analyses. L.G.S., A.F., A.C.d.A.P. and G.B. prepared all figures and tables. L.G.S., R.C. and G.B. wrote the main manuscript. All authors reviewed the manuscript.

Additional Information

Competing financial interests: The authors declare no competing financial interests.

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4.3 PARTE III – Em processo de revisão

Tridimensional dose parameters of pelvic organs at risk are predictors of acute clinical toxicity in vaginal vault high-dose rate brachytherapy

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5 CONCLUSÃO

As principais conclusões do estudo são:

- ✓ A aferição da dose no ponto de bexiga D_{ICRU} sofre distorções por conta de diferenças na tensão aplicada no cateter de Foley colocado na bexiga. Adicionalmente, no cenário da braquiterapia de cúpula vaginal isolada, o risco de infecção decorrente da colocação do cateter possivelmente suplanta o beneficio da documentação da dose, por conta dos baixos índices de toxicidade aguda relacionada ao tratamento.
- ✓ Os parâmetros volumétricos de dose na bexiga, trígono vesical e uretra são possíveis preditores de toxicidade urinaria aguda na braquiterapia de cúpula vaginal.
- ✓ O ponto de dose no reto D_{ICRU} não se relacionou com a incidência de toxicidade aguda intestinal, em oposição aos parâmetros volumétricos reto D1.0cc e D2.0cc, além da D_{MAX} no cólon sigmoide.

Nossa expectativa é que a metodologia e os resultados deste estudo contribuam para o aprimoramento da informação de dose em órgãos de risco.

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Anexo 1 - Carta de aprovação do Comitê de Ética em Pesquisa-CEP AC-G01-R

A.C.Camargo Cancer Center

FUNDAÇÃO ANTÔNIO PRUDENTE-HOSPITAL DO CÂNCER A C CAMARGO

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Análise retrospectiva uni-institucional dos casos de neoplasia maligna de endométrio tratados com braquiterapia adjuvante exclusiva - Toxicidade e desfechos oncológicos

Pesquisador: Glauco Baiocchi Neto

Área Temática:

Versão: 2

CAAE: 41653115.2.0000.5432

Instituição Proponente: Fundação Antônio Prudente-Hospital do Câncer-A C Camargo

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.026.042

Data da Relatoria: 14/04/2015

Apresentação do Projeto:

Trata-se da análise após respostas de pendências geradas no parecer número 969.146.

Objetivo da Pesquisa:

Os objetivos do projeto de pesquisa foram revistos apresentando-se adequados aos desenho do estudo.

Avaliação dos Riscos e Benefícios:

Trata-se da análise após respostas de pendências geradas no parecer número 969.146.

Comentários e Considerações sobre a Pesquisa:

Trata-se da análise após respostas de pendências geradas no parecer número 969.146.

Considerações sobre os Termos de apresentação obrigatória:

Trata-se da análise após respostas de pendências geradas no parecer número 969.146.

Recomendações:

Trata-se da análise após respostas de pendências geradas no parecer número 969.146.

Conclusões ou Pendências e Lista de Inadequações:

Aprovado

Endereço: Rua Professor Antônio Prudente, 211
Bairro: Liberdade **CEP:** 01.509-900
UF: SP **Município:** SAO PAULO
Telefone: (11)2189-5020 **Fax:** (11)2189-5020 **E-mail:** cep_hcancer@accamargo.org.br

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

Nota: Informações a respeito do andamento do referido projeto deverão ser encaminhadas ao CEP dentro de 06 meses a partir desta data em relatório (modelo CEP).

SAO PAULO, 16 de Abril de 2015

Assinado por:
Jefferson Luiz Gross
(Coordenador)

Endereço: Rua Professor Antônio Prudente, 211
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Anexo 2 - Carta de aprovação do Comitê de Ética em Pesquisa-CEP AC-G01-P

A.C.Camargo Cancer Center

Comitê de Ética em Pesquisa - CEP

São Paulo, 12 de março de 2014.

Ao
Dr. Glauco Baiocchi Neto.

Ref.: Projeto de Pesquisa nº. 1866/14
"Análise clínico-dosimétrica da dose em bexiga e reto na braquiterapia ginecológica de alta taxa de dose baseada em planejamento em três dimensões".

Os membros do Comitê de Ética em Pesquisa em Seres Humanos da Fundação Antonio Prudente – Hospital do Câncer - A.C. Camargo/SP, em sua última reunião de 11/03/2014, após analisarem as respostas aos questionamentos realizados em reunião de 11/02/2014, **aprovaram** a realização do projeto (datado de 2014), o Termo de Consentimento Livre e Esclarecido e tomaram conhecimento dos seguintes documentos:

- Folha de Rosto para Pesquisa Envolvendo Seres Humanos;
- Termo de Compromisso do Pesquisador com Resoluções do Conselho Nacional de Saúde;
- Declaração Sobre o Plano de Recrutamento dos Sujeitos de Pesquisa, Circunstâncias e Responsáveis Pela Obtenção do TCLE;
- Declaração Sobre os Dados Coletados, Publicação dos Dados e Propriedade das Informações Geradas;
- Declaração de Ciência e Comprometimento do Departamento de Ginecologia Oncológica;
- Declaração de Ciência e Comprometimento do Departamento de Radioterapia;
- Declaração de Ciência e Comprometimento do Departamento de Radiologia;
- Declaração de Intraestrutura e Instalações do Departamento de Ginecologia Oncológica;
- Declaração de Intraestrutura e Instalações do Departamento de Radioterapia;
- Declaração de Intraestrutura e Instalações do Departamento de Radiologia;
- Cronograma do Estudo;
- Orçamento Financeiro Detalhado;

Informações a respeito do andamento do referido projeto deverão ser encaminhadas ao CEP dentro de 06 meses em relatório (modelo CEP).

Atenciosamente,

Dr. Antônio Hugo José Fróes Marques Campos
2º Vice-Coordenador do Comitê de Ética em Pesquisa

1/1

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Anexo 3 - Carta de aprovação do Comitê de Ética em Pesquisa-CEP da mudança de nível do projeto

A.C.Camargo Cancer Center

Comitê de Ética em Pesquisa - CEP

São Paulo, 08 de outubro de 2015.

Ao
Dr. Glauco Baiocchi Neto

Ref.: Projeto de Pesquisa nº. 1866/14
"Análise clínico-dosimétrica da dose em bexiga e reto na braquiterapia ginecológica de alta taxa de dose baseada em planejamento em três dimensões".

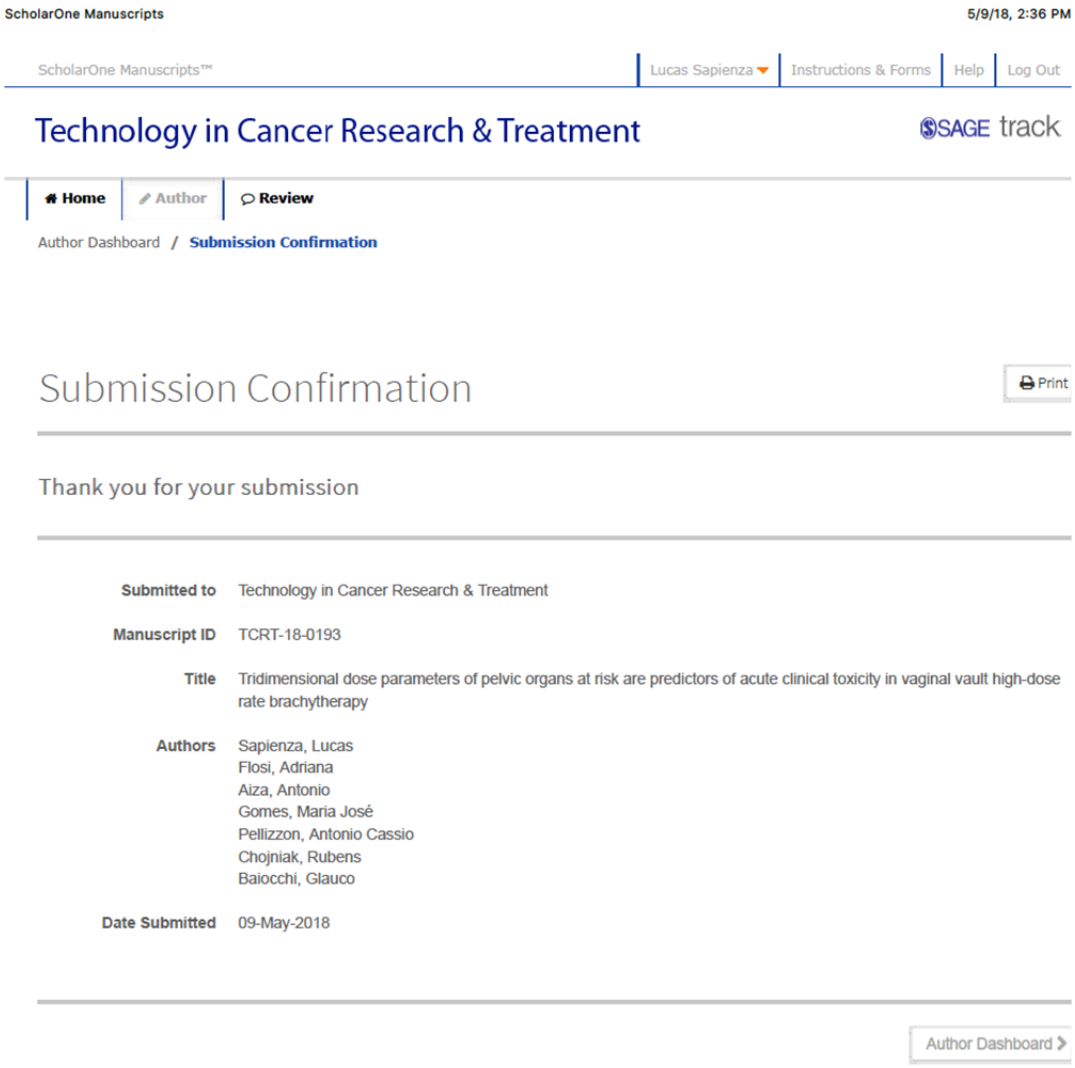
Os membros do Comitê de Ética em Pesquisa em Seres Humanos da Fundação Antonio Prudente – Hospital do Câncer - A.C. Camargo/SP, em sua última reunião de 06/10/2015, **tomaram conhecimento** do seguinte documento:

- Mudança do nível do projeto de Departamental para Mestrado do aluno Lucas Gomes Sapienza, em documento datado de 10 de setembro de 2015

Atenciosamente,

Dr. Jefferson Luiz Gross
1º Vice-Coordenador do Comitê de Ética em Pesquisa

Anexo 4 - Declaração de submissão de artigo à revista científica



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Thank you for your submission

Submitted to	Technology in Cancer Research & Treatment
Manuscript ID	TCRT-18-0193
Title	Tridimensional dose parameters of pelvic organs at risk are predictors of acute clinical toxicity in vaginal vault high-dose rate brachytherapy
Authors	Sapienza, Lucas Flosi, Adriana Aiza, Antonio Gomes, Maria José Pellizzon, Antonio Cassio Chojniak, Rubens Baiocchi, Glauco
Date Submitted	09-May-2018

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