ANA FRANCISCA VAZ

QUALIDADE DE VIDA E EVENTOS ADVERSOS APÓS A RADIOTERAPIA EM MULHERES COM CÂNCER GINECOLÓGICO: UM ESTUDO DE COORTE PROSPECTIVO

Tese de Doutorado

ORIENTADOR: Prof. Dr. AARÃO MENDES PINTO-NETO

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2011

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Tese apresentada ao Programa de Pós-Graduação em Tocoginecologia, da Faculdade de Ciências Médicas da Universidade Estadual de Campinas para obtenção do título de Doutor em Ciências da Saúde, área de concentração: Fisiopatologia Ginecológica.

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FICHA CATALOGRÁFICA ELABORADA PELA
BIBLIOTECA DA FACULDADE DE CIÊNCIAS MÉDICAS
UNICAMP
Bibliotecária: Rosana Evangelista Poderoso – CRB-8ª / 6652

V477q

Vaz, Ana Francisca
Qualidade de vida e eventos adversos após a radioterapia em mulheres com câncer ginecológico: um estudo de coorte prospectivo / Ana Francisca Vaz. – Campinas, SP: [s.n.], 2011.

Orientador: Aarão Mendes Pinto-Neto
Tese (Doutorado) – Universidade Estadual de Campinas, Faculdade de Ciências Médicas.

1. Câncer. 2. Colo uterino. 3. Endométrio. 4. Radioterapia. 5. Qualidade de vida. 6. Efeitos colaterais. 7. Menopausa. 8. Sexualidade. I. Pinto-Neto, Aarão Mendes. II. Universidade Estadual de Campinas. Faculdade de Ciências Médicas. III. Título.

Título em Inglês: Quality of life and adverse events after radiotherapy in gynecologic cancer survivors: a cohort study

Keywords:
- Cancer
- Cervix uteri
- Endometrium
- Radiotherapy
- Quality of life
- Adverse effects
- Menopause
- Sexuality

Titulação: Doutor em Ciências da Saúde
Área de Concentração: Fisiopatologia Ginecológica

Banca examinadora:
Prof. Dr. Aarão Mendes Pinto-Neto
Prof. Dr. Luiz Carlos Zeferino
Profª. Drª. Maria Salete Costa Gurgel
Prof. Dr. José Maria Soares Junior
Profª. Drª. Ana Carolina Japur de Sá Rosa e Silva

Data da defesa: 25 – 05 – 2011

Diagramação e arte final: Assessoria Técnica do CAISM (ASTEC)

BANCA EXAMINADORA DA TESE DE DOUTORADO

Aluno: ANA FRANCISCA VAZ

Orientador: Prof. Dr. AARÃO MENDES PINTO-NETO

Membros:

1.
2.
3.
4.
5.

Curso de Pós-Graduação em Tocoginecologia da Faculdade de Ciências Médicas da Universidade Estadual de Campinas

Data: 25/05/2011

Dedico este trabalho...

*...**Aos meus pais**,*
Joaquim Vaz (in memoriam) e Rosa Maria,
pelo exemplo de amor à família,
apoio e dedicação ao longo de minha vida.

*...**Ao meu marido***
Flávio, pelo incentivo, dedicação e paciência nos momentos difíceis.

...À minha filha
Mitie, pelo carinho e por tentar entender
os momentos em que não estive presente.

*...**Às minhas irmãs***
Maria e Laura, que sempre acreditaram em mim.

Às mulheres
com câncer ginecológico que gentilmente concordaram em participar do estudo.

Agradecimentos

Ao Prof. Dr. Aarão Mendes Pinto-Neto pela amizade, paciência, apoio e incentivo em todos esses anos. Amigo e "Professor orientador" em todos os momentos, principalmente nos mais difíceis, e pelo exemplo de espírito científico.

Aos Professores-Doutores do programa de Pós-graduação do Departamento de Tocoginecologia pela dedicação e incentivo durante o curso.

Ao amigo Délio Conde pela contribuição inestimável para a realização deste trabalho.

À Dra. Adriana O. Pedro por contribuir para a elaboração da apresentação oral e de pôster e por apresentar o trabalho em congressos.

Ao Dr. Sérgio Esteves pelas orientações especializadas referentes à radioterapia.

À enfermeira Regina Grion pela amizade e colaboração que permitiu conciliar o trabalho e a realização deste estudo.

Aos funcionários e amigos da Radioterapia que contribuíram para a realização deste estudo.

Ao Daniel, da secretaria da Radioterapia, pela colaboração em relação ao agendamento e na localização dos prontuários médicos.

À Vanda, bibliotecária, pela contribuição com os artigos.

Ao Lúcio Tito Gurgel pela contribuição quando solicitado.

Sumário

Símbolos, Siglas e Abreviaturas

CAISM – Centro de Atenção Integral à Saúde da Mulher

CTC v2.0 – *Common Toxicity Criteria, version 2.0*

CTCAE v 3.0 – *Common Terminology Criteria for Adverse Events, version 3.0*

EP – *Estimated Parameter*

FIGO – *International Federation of Gynecology and Obstetrics*

Lent-Soma – *Late Effects of Normal Tissue*

QOL – *Quality of life*

QV – Qualidade de Vida

R^2 – *Coefficient of Determination*

RT – *Radiotherapy*

RTOG/ EORTC – *Toxicity Criteria of the Radiotherapy Oncology Group and European Organization for Research and Treatment of Cancer*

SD – *Standard Deviations*

SEM – *Structural Equation Models*

TH – Terapia Hormonal / *Hormone Therapy*

UNICAMP – Universidade Estadual de Campinas

WHOQOL-BREF – *World Health Organization's Quality of Life instrument*

(WHOQOL-breve) – *Questionário de Avaliação de Qualidade de Vida da Organização Mundial da Saúde*

Resumo

Objetivos: Investigar a frequência de eventos adversos antes e após a radioterapia, a proporção de mulheres sexualmente ativas, avaliar a qualidade de vida (QV) e identificar seus preditores em uma coorte de mulheres com câncer ginecológico. **Métodos:** Estudo de coorte prospectivo com 107 mulheres com câncer ginecológico (colo do útero ou endométrio), idade (21 a 75) anos, tratadas com radioterapia, 89 (teleterapia e braquiterapia) 10 (braquiterapia) 8 (teleterapia) no Hospital da Mulher Prof. Dr. José Aristodemo Pinotti CAISM/UNICAMP. A QV foi avaliada através do questionário da Organização Mundial da Saúde - (WHOQOL-breve), antes da radioterapia (T0), 4 meses (T1), 1ano (T2) e 3 anos (T3) após o tratamento. Os eventos adversos após a radioterapia foram graduados de acordo com a escala Common Terminology Criteria Adverse Event (CTCAE) v 3.0. Os escores de QV foram avaliados através do teste de Wilcoxon pareado e os seus preditores identificados por meio de regressão linear. Utilizou-se o teste de McNemar para avaliar as diferenças entre as frequências de sintomas sexuais e da menopausa, e da proporção de mulheres sexualmente ativas após a radioterapia em relação à avaliação inicial. **Resultados**: A mediana da idade das participantes antes da radioterapia foi 60 anos. O domínio meio ambiente e a saúde geral eram os

mais comprometidos antes da radioterapia. Dor (49,5%) e sangramento vaginal (36,9%) foram as queixas mais frequentes. Anemia ($p<0,01$) e náusea e/ou vômito ($p=0,01$) interferiram negativamente no domínio físico; dor no domínio físico ($p<0,01$), QV global ($p=0,02$) e saúde geral ($p=0,01$), e história de cirurgia positivamente na saúde geral ($p<0,01$). Três anos após a radioterapia observou-se uma redução da frequência de secura vaginal (26,7% em T0 vs 8,3% em T3; $p<0,005$), aumento da proporção de mulheres sexualmente ativas (21,5% em T0 vs 44,2% em T3; $p=0,005$) em relação à avaliação inicial, e aumento significativo dos escores de QV para o domínio psicológico, saúde geral e QV global. Dor associou-se negativamente com os domínios físico, psicológico e relacionamento social ($p<0,05$); dispareunia com os domínios físico e relacionamento social ($p<0,05$); diminuição do interesse sexual com o domínio psicológico ($p<0,01$) e maior renda positivamente com o domínio psicológico e saúde geral ($p<0,05$). **Conclusão**: O domínio meio ambiente e a questão relacionada à saúde eram os mais prejudicados antes da radioterapia. Os sintomas do câncer foram os fatores de maior interferência na QV. Três anos após a radioterapia verificou-se melhora da QV e aumento significativo do número de mulheres sexualmente ativas em relação à avaliação prévia. A presença de dor, dispareunia e diminuição do interesse sexual interferiram negativamente na QV.

Palavras-chave: Câncer ginecológico, Qualidade de vida, Eventos adversos, Função sexual, Radioterapia.

Summary

Objectives: To investigate the frequency of adverse events before and after radiotherapy, the proportion of sexually active women, evaluate quality of life (QOL) and identify their predictors in a cohort of women with gynecologic cancer. **Methods:** A prospective cohort study of 107 women with gynecologic cancer (cervical or endometrial), aged (21 to 75) years, treated with radiotherapy, 89 (teletherapy and brachytherapy) 10 (brachytherapy) 8 (teletherapy) in the Prof. Dr. José Aristodemo Pinotti Women's Hospital-CAISM/UNICAMP. QOL was assessed by the World Health Organization- (WHOQOL-BREF) questionnaire, before radiotherapy (T0), 4 months (T1),1year (T2) and 3 years (T3) after treatment. The adverse events following radiotherapy were scored according to the Common Terminology Criteria Adverse Event (CTCAE) scale, v 3.0. QOL scores were assessed by the paired Wilcoxon test and their predictors were identified by linear regression analysis. The McNemar test was used to assess the differences between the frequencies of sexual symptoms and menopause, as well as the proportion of sexually active women after radiotherapy compared to baseline evaluation. **Results**: The median age of the participants before radiotherapy was 60 years. The environmental domain and general health were the most impaired

before radiotherapy. Pain (49.5%) and vaginal bleeding (36.9%) were the most frequent complaints encountered. Anemia ($p<0.01$), nausea and/or vomiting ($p=0.01$) negatively interfered with the physical domain. Pain negatively interfered with the physical domain ($p<0.01$), global QOL ($p=0.02$) and general health ($p=0.01$). A history of surgery positively interfered with general health ($p<0.01$). Three years after radiotherapy, there was a decrease in the frequency of vaginal dryness (26.7% in T0 vs 8.3% in T3; $p<0.005$), an increase in the proportion of sexually active women (21.5% in T0 vs 44.2% in T3; $p=0.005$) in comparison to baseline assessment, and a significant increase in QOL scores for the psychological domain, general health and global QOL. Pain was negatively associated with the physical, psychological and social relationship domains ($p<0.05$). Dyspareunia was negatively associated with the physical and social relationship domains ($p<0.05$). Decreased sexual interest was negatively associated with the psychological domain ($p<0.01$). A higher income was positively associated with the psychological domain and general health ($p<0.05$). **Conclusion**: The environmental domain and the question related to general health were the most compromised before radiotherapy. Cancer symptoms were the factors that most interfered with QOL. Three years after radiotherapy, there was an improvement in QOL and a significant increase in the number of sexually active women compared to prior evaluation. Pain, dyspareunia and decreased sexual interest negatively interfered with QOL.

Keywords: Gynecologic cancer, Quality of life, Adverse events, Sexual function, Radiotherapy.

1. Introdução

O câncer ginecológico representa um grupo de neoplasias malignas muito frequente em mulheres. Entre os tumores desse grupo o câncer do colo do útero é a segunda neoplasia mais frequente (1), com incidência cerca de duas vezes maior em países menos desenvolvidos quando comparados com os mais desenvolvidos (2). Em contraste, o câncer do endométrio é mais frequente em países desenvolvidos onde ocupa o sétimo lugar entre as neoplasias em mulheres no mundo (1,3). No Brasil, o câncer do colo do útero é a terceira neoplasia entre as mulheres, sendo estimados 18.430 casos novos para 2010. O câncer do endométrio não está entre as quatro neoplasias mais frequentes (2).

Para o tratamento do câncer ginecológico usualmente as modalidades de tratamento mais utilizadas são cirurgia, radioterapia e quimioterapia (4). O tratamento recomendado para o câncer do colo do útero em estágios iniciais é a histerectomia total abdominal com linfadenectomia pélvica, com ou sem quimioterapia e radioterapia adjuvante – dependendo dos fatores associados – e para os casos mais avançados quimioterapia e radioterapia concomitante (5).

Para o câncer do endométrio recomenda-se estadiamento completo com histerectomia total/salpingooforectomia bilateral, com dissecção de linfonodos pélvicos e paraórticos (6). O tratamento adjuvante com quimioterapia, radioterapia, ou combinação de ambos, geralmente é usado para os casos mais avançados (5). Náuseas, fadiga, sangramento vaginal, anemia, estenose vaginal e fístulas vesicovaginais e retovaginais são complicações relacionadas ao tratamento e à progressão da doença. Além dessas alterações, distúrbios do sono (7), ideação suicida (8), sintomas climatéricos e alterações da função sexual (9,10) foram reportados por mulheres com câncer ginecológico. Esses sintomas podem contribuir para uma percepção negativa da qualidade de vida (QV).

A associação entre modalidades de tratamento vem sendo cada vez mais utilizada para a melhora da sobrevida (11,12). Contudo, a radioterapia está relacionada ao aparecimento de efeitos adversos tardios, principalmente na região pélvica (13), que são definidos como aqueles que ocorrem três meses após o tratamento radioterápico (14). Apesar da tendência no aumento da associação de diferentes modalidades de tratamento para o câncer ginecológico, há falta de dados quanto à incidência de efeitos adversos tardios ao longo do tempo e de sua interferência na QV (15).

Estudos prévios relataram que para pacientes com câncer do colo uterino em estádio avançado, o tratamento com radioterapia associada à quimioterapia levou a aumento na taxa total de sobrevida e livre de doença (16,17,18). Avaliando o efeito de quimioterapia e radioterapia concomitante para o tratamento do câncer do colo do útero em uma revisão sistemática, onde foram incluídas 4921 pacientes, foi

observada forte evidência de melhora da sobrevida total e livre de doença (18). Contudo, não foi possível determinar adequadamente o impacto da associação da radioterapia e quimioterapia nos efeitos adversos tardios do tratamento.

A radioterapia pélvica está associada a alterações nos tratos gastrintestinal, urinário, ginecológico e ovário, resultando em efeitos tardios como diarreia, incontinência urinária, disúria, dor, sangramento vaginal, vesical e retal, hematúria, ondas de calor, secura vaginal, estenose, atrofia e encurtamento vaginal, perda da elasticidade vaginal, dispareunia, diminuição do interesse sexual (19-22). Diarreia foi o efeito adverso tardio mais frequente em pacientes com câncer ginecológico tratadas com radioterapia (23) que tende a se tornar um problema crônico (24). Diarreia foi referida por 43,2% das pacientes com câncer cervical após a radioterapia (25).

Incontinência urinária foi observada em 25,2% das pacientes com câncer do colo do útero tratadas com radioterapia ou cirurgia após 25-86 meses do tratamento e disúria em 14,4% das pacientes tratadas com radioterapia e em 41,8% naquelas tratadas com cirurgia (25). Comparando sintomas climatéricos, urinários e sexuais em mulheres com câncer do endométrio ou cervical, tratadas com radioterapia, com pacientes histerectomizadas por doenças benignas um ano após o tratamento, a incontinência urinária foi o sintoma mais comum nos três grupos (26).

Dor é um evento adverso frequente em pacientes com câncer ginecológico. Taxas elevadas de dores pélvica e lombar (29%) foram observadas em pacientes

com câncer cervical tratadas com radioterapia (27) e taxas de dor abdominal foram observadas em 22,5% das pacientes tratadas com cirurgia ou radioterapia (25).

Tratamentos para o câncer podem resultar em morbidade aguda e crônica no trato genital feminino, ocasionando efeitos intensos e frequentemente irreversíveis na capacidade reprodutiva, integridade endócrina e na função sexual. As células em divisão da granulosa, em crescimento nos folículos ovarianos para maturação dos oócitos, são as mais danificadas pela radiação. Picnose pode ser vista nas células da granulosa em poucas horas após a radioterapia, precedendo as alterações morfológicas do oócito. Com a destruição das células da granulosa o óvulo perde a viabilidade e o folículo torna-se atrófico. Em mulheres em que a dose da radioterapia foi suficiente para causar esterilidade permanente (acima de 24 Gy), os ovários revelam desaparecimento total ou quase total dos folículos primordiais, às vezes acompanhado de resquícios de atresia e atrofia folicular. Há também a perda de células normais do estroma cortical com diminuição do ovário, sendo a córtex ovariana amplamente substituída por colágeno (28).

Os efeitos da radioterapia nos ovários são esterilidade e insuficiência endócrina. Pacientes na pré-menopausa com ovários intactos podem apresentar ondas de calor durante e após o tratamento (28). Dependendo da localização e extensão da doença, a radioterapia pélvica é administrada localmente ou em grandes áreas, sendo altamente efetiva, mas resulta na perda da função ovariana (29).

A transposição ovariana utilizando laparotomia ou laparoscopia é indicada para evitar a irradiação do ovário em pacientes jovens (29) e em estádios iniciais

do câncer cervical (30). Entretanto, a função ovariana foi preservada com a transposição ovariana em apenas 50% das 28 mulheres tratadas com radioterapia pós-cirurgia por câncer cervical estádio I-IIA, 14 pacientes referiram sintomas da menopausa, sendo tratadas com terapia de reposição hormonal (31).

Os parâmetros mensuráveis para disfunção sexual são: dispareunia, secura vaginal, estenose/ encurtamento vaginal, sinéquia, frequência, interesse, satisfação na relação sexual e orgasmo. As alterações crônicas na vagina incluem diminuição e atrofia do epitélio vaginal, resultando na diminuição do canal vaginal devido ao encurtamento, estreitamento, perda da elasticidade e fibrose da parede vaginal. O exame microscópico das camadas submucosa e muscular da vagina após a irradiação mostra hialinização, colagenização, perda do tecido conjuntivo, ausência de pequenas glândulas de lubrificação vaginal, estreitamento e obliteração do lúmen de pequenos vasos sanguíneos, e substituição das fibras musculares por fibrose (28).

Avaliando os efeitos da radioterapia e cirurgia na função sexual de mulheres com câncer cervical, Flay et al. (27) relataram que metade das pacientes apresentou disfunção sexual devido aos efeitos da radioterapia. Dispareunia, secura vaginal e estreitamento vaginal foram observados em 43% das pacientes 14 semanas após a radioterapia, e encurtamento vaginal em 64%.

Avaliando sintomas urinários, climatéricos e sexuais em pacientes com câncer cervical, em que a maioria foi tratada com radioterapia e cirurgia sem braquiterapia, não foi observado aumento de urgência, incontinência urinária,

sudorese e ondas de calor um ano após o tratamento em relação à avaliação prévia. Entretanto, houve um aumento significativo de mulheres em uso de TH um ano após o tratamento em relação a antes do tratamento. Observou-se aumento para secura vaginal e dispareunia, sendo esse aumento significativo apenas para dispareunia (32).

Descrevendo função sexual e alterações em vagina por um período de dois anos em 118 pacientes com câncer cervical tratadas com radioterapia, Jensem et al. (22) observaram que 53% das pacientes eram sexualmente ativas. Aproximadamente 85% referiram pouco ou nenhum interesse sexual, 35% moderada a intensa diminuição na lubrificação, 55% média a severa dispareunia, 30% estavam insatisfeitas com sua vida sexual e 50% referiram redução da dimensão vaginal. Após o tratamento, 63% das pacientes sexualmente ativas antes do tratamento continuavam sexualmente ativas.

A interferência de efeitos adversos tardios da radioterapia (menopausa, dispareunia, secura vaginal, estenose e encurtamento vaginal, atrofia e perda da elasticidade vaginal) na função sexual de mulheres com câncer do colo do útero está bem estabelecida (21, 22, 27,33,10,34), resultando em considerável distress (33), mas para o câncer do endométrio continua sendo pouco pesquisada (35), embora estudos prévios relatem interferência negativa de certos efeitos tardios da radioterapia na função sexual de mulheres com câncer ginecológico (36) e do colo do útero (22, 27,33). Contudo, apenas alguns desses estudos incluíram mulheres em estágio mais avançado da doença (III/IV), realizaram avaliação inicial e avaliaram a função sexual prospectivamente (22, 27). Esses

fatores podem comprometer a avaliação da interferência da radioterapia na função sexual e dificultar a comparação entre os estudos.

A incidência dos efeitos tardios da radioterapia está relacionada com a dose total da radioterapia (37), fração de dose (38), volume irradiado (39) e com as técnicas usadas (40). Contudo, a comparação da incidência desses efeitos entre os estudos tem sido dificultada pelos diferentes métodos de avaliação usados, devido aos estudos serem geralmente retrospectivos, não avaliarem a ocorrência de efeitos leves, e por utilizarem diferentes escalas para classificar esses efeitos (11,41).

As escalas mais utilizadas para a graduação de efeitos da radioterapia são Toxicity Criteria of the Radiotherapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) (42), Late Effects of Normal Tissue (Lent-Soma) (43) e Common Toxicity Criteria, Version 2.0 (CTC) (44).

Em 2003 foi desenvolvida uma escala mais abrangente para graduar eventos adversos relacionados aos tratamentos do câncer, denominada Common Criteria for Adveres Events version 3.0 (CTCAEv3.0) (45), que inclui tanto os efeitos agudos como os tardios. A escolha da escala (CTCAEv3.0) (45) para avaliar os efeitos tardios da radioterapia ocorreu por ela ser mais abrangente, permitindo a avaliação de eventos adversos gastrointestinais, urinários, da menopausa, sexuais e dor, que foram avaliados nessa fase do estudo. A graduação dessa escala é de 1 a 5, de uma forma simplificada, em que 1 significa evento adverso leve, 2 moderado,

3 intenso, 4 incapacitante e 5 morte. A graduação para diarreia e sangramento é de 1 a 5, para dispareunia, incontinência urinária, disúria e dor de 1 a 4, para ondas de calor de 1 a 3 e para diminuição do interesse sexual e secura vaginal de 1 a 2.

A estimativa média mundial de cinco anos de sobrevida para o câncer do colo do útero é de 49% (2) e a taxa relativa de cinco anos de sobrevida para o câncer do corpo do útero de 84,1%, para os Estados Unidos, e 76% para a Europa (3). Considerando que as taxas de cinco anos de sobrevida em pacientes com câncer do colo do útero e do endométrio são relativamente boas, a avaliação da QV dessas mulheres tem-se tornado muito importante (46), pois o tratamento de radioterapia está mais associado à piora da QV em relação à quimioterapia e cirurgia (47).

A avaliação da QV tem sido incluída como mais um fator para avaliação de resultados em muitos ensaios clínicos (48). Apesar de amplamente utilizada, não há um consenso para definição do termo QV, já que inclui vários componentes, como domínios físico, funcional, emocional, social e cognitivo (49). A definição de QV é subjetiva porque engloba aspectos socioculturais da população estudada e a percepção individual do estado de saúde (50).

Estudos que avaliaram prospectivamente a QV de pacientes com câncer ginecológico geralmente relatam prejuízo na QV durante e no final da radioterapia, com melhora após o tratamento (51-53). Entretanto, piora da QV associada à radioterapia tem sido relatada em pacientes com câncer ginecológico (4, 54) e

efeito negativo de certos eventos adversos tardios na QV até pelo menos dois anos após a radioterapia (55).

Os efeitos agudos da radioterapia geralmente são de curta duração e habitualmente melhoram com medicações, enquanto os tardios são frequentemente irreversíveis, prejudicando a QV por longos períodos e, em alguns casos, permanentemente (11). Associação negativa entre alguns efeitos tardios da radioterapia pélvica (dor, diarreia, dispareunia e diminuição do interesse sexual) e QV foi observada em pacientes com câncer ginecológico após o tratamento (23,56). A ocorrência de diarreia foi o sintoma mais comum 3 a 4 anos após o tratamento de radioterapia com interferência negativa na QV de pacientes com câncer ginecológico (23). Associação negativa entre dor e QV foi observada em pacientes com câncer ginecológico antes (57) e após a radioterapia (23). Diminuição do interesse sexual e dispareunia estavam negativamente associadas com a QV em mulheres com câncer cervical após diferentes modalidades de tratamento, incluindo o tratamento radioterápico (56).

De acordo com alguns autores, as características sociodemográficas exercem pouca influência na QV de pacientes com câncer quando outras variáveis são consideradas (58). As variáveis sociodemográficas (renda, idade, escolaridade, cor) não se associaram à QV de mulheres com câncer ginecológico antes (57) e após o tratamento (46); contudo a real interferência desses fatores na QV tem sido pouco avaliada prospectivamente.

Considerando que os estudos relacionados à QV de mulheres com câncer ginecológico e eventos adversos antes e após a radioterapia foram realizados em países desenvolvidos com diferentes realidades socioculturais, onde existem escassas informações provenientes de estudos longitudinais sobre esse tema e não foi identificado nenhum estudo nacional sobre esse assunto, realizou-se esta pesquisa que teve como objetivo: Investigar a frequência de eventos adversos antes e após a radioterapia, a proporção de mulheres sexualmente ativas, avaliar prospectivamente a qualidade de vida (QV) e identificar seus preditores em uma *coorte* de mulheres com câncer ginecológico (colo do útero ou endométrio) tratadas no Hospital da Mulher Prof. Dr. José Aristodemo Pinotti CAISM/UNICAMP, de março de 2005 a março de 2009.

2. Objetivos

2.1. Objetivo Geral

Investigar a frequência de eventos adversos antes e após a radioterapia, a proporção de mulheres sexualmente ativas, avaliar prospectivamente a qualidade de vida (QV) e identificar seus preditores em uma coorte de mulheres com câncer ginecológico.

2.2. Objetivos Específicos

- Avaliar a QV e identificar seus fatores associados antes do início da radioterapia.
- Investigar a proporção de mulheres sexualmente ativas, a frequência de sintomas sexuais e da menopausa antes e após a radioterapia, avaliar a QV identificando os seus preditores.
- Avaliar a QV após a radioterapia, investigar a frequência de eventos adversos e a associação desses sintomas com a QV.

3. Publicações

Artigo 1 – **Quality of Life of Women with Gynecologic Cancer: Associated Factors**

Running title: Quality of Life of Women with Gynecologic Cancer

Artigo 2 – **Quality of Life, Menopause and Sexual Symptoms in Gynecologic Cancer Survivors: a cohort study**

Running title: QOL, menopausal symptoms and Gynecol. Cancer

Artigo 3 – **Quality of Life and Adverse Events after Radiotherapy in Ginecologic Cancer Survivors: a cohort study**

3.1. Artigo 1

From: "Hans Ludwig" <prof.ludwig@bluewin.ch>
To: <condedelio@uol.com.br>
Cc: <Bitzer@mx.uol.com.br>
Sent: Monday, May 21, 2007 10:04 AM
Subject: Your Submission ARCH-07-384R1

> Dear Dr. Délio Marques Conde,
>
> We are pleased to inform you that your manuscript, "Quality of Life of
> Women with Gynecologic Cancer: Associated Factors", has been accepted for
> publication in Archives of Gynecology and Obstetrics.
>
> You will be contacted about proofs and offprints in due course by our
> Production Department.
>
> If you would like to have your accepted article published with open access
> in our Open Choice program, please access the following URL:
> http://www.springer.com/openchoice
>
> Please remember to quote the manuscript number, ARCH-07-384R1, whenever
> inquiring about your manuscript.
>
> With best regards,
> Hans Ludwig
>
>
> We have seen your comments to the reviews received and accept the paper as
> it now (R1) stands. Kind regards, Hans Ludwig
>

Quality of Life of Women with Gynecologic Cancer: Associated Factors

Running title: Quality of Life of Women with Gynecologic Cancer

Ana F. Vaz[1], Aarão M. Pinto-Neto[1], Délio M. Conde[2],
Lúcia Costa-Paiva[1], Sirlei S. Morais[1], Sérgio B. Esteves[1]

[1]Department of Gynecology and Obstetrics, Universidade Estadual de Campinas, School of Medicine, Campinas, Brazil

[2]Department of Gynecology and Obstetrics, Universidade Federal de Goiás, School of Medicine, Goiânia, Brazil

Correspondence: Aarão M. Pinto-Neto. Department of Gynecology and Obstetrics, Universidade Estadual de Campinas. Rua Alexander Fleming, 101, Cidade Universitária ‘‘Zeferino Vaz’’, 13083-970, Campinas, SP, Brazil.

Phone/Fax: +55 19 3521 9306; E-mail address: aarao@unicamp.br

Abstract

Objective: To evaluate quality of life (QOL) and identify its associated factors in a cohort of women with gynecologic cancer. **Methods:** A cross-sectional study was conducted, including 103 women with cervical or endometrial cancer, aged between 18 and 75 years who were receiving their entire treatment at the institution where the investigation was carried out. QOL was measured by the World Health Organization's Quality of Life instrument-abbreviated version (WHOQOL-BREF). Clinical and sociodemographic characteristics, in addition to prevalence of cancer-related symptoms prior to radiotherapy were investigated. Bivariate analysis was performed, applying the Mann-Whitney test. Multivariate analysis was used to identify factors associated with QOL. **Results**: The mean age of the participants was 56.8±11.6 years. The study included 67 (65%) women with cervical cancer and 36 (35%) women with endometrial cancer. Most participants were at an advanced stage (63.1%). The most common complaints were pain (49.5%) and vaginal bleeding (36.9%). The prevalence of anemia was 22.3%. On multivariate analysis, it was observed that anemia (p=0.006) and nausea and/or vomiting (p=0.010) determined impairment in physical domain. Pain negatively influenced physical domain (p=0.001), overall QOL (p=0.024) and general health (p=0.013), while the history of surgery positively affected general health (p=0.001). **Conclusion:** Cancer-related symptoms were factors that most interfered with QOL in women with gynecologic cancer. Therefore, more attention should be focused on identifying these symptoms, adopting measures to minimize their repercussions on QOL.

Keywords: Cervical cancer, Endometrial cancer, WHOQOL-BREF questionnaire, Anemia, Pain.

Introduction

Gynecologic cancer is one of the most frequent groups of malignancies. Among the tumors in this group, cervical cancer is the second most common malignancy among women, occurring mainly in developing countries. In contrast, endometrial cancer is more frequent in developed countries [1]. In Brazil, 19,260 new cases of cervical cancer are expected for the year 2006 [2]. Despite the advances made in screening for these malignancies, a significant number of cases are still diagnosed in an advanced stage, contributing for the high morbidity.

Diagnosis at late cancer stages requires a combination of different therapeutic modalities such as surgery, radiotherapy and chemotherapy. Nausea, fatigue, vaginal bleeding, anemia, vesicovaginal and rectal-vaginal fistulas are some complications related to treatment and progression of the disease. In addition to these alterations, sleep disorders [3], suicidal ideation [4], climacteric symptoms and compromise of sexual function [5, 6] have been reported among women with gynecologic cancer. These symptoms may contribute towards a negative perception of quality of life (QOL).

Previous studies have demonstrated an impairment in various QOL dimensions in women with gynecologic cancer [5-8], identifying some predictors of QOL such as pretreatment health conditions [7]. The results of these studies suggest that QOL in women treated for gynecologic cancer tends to improve with the passage of time [3, 5]. The longer the interval since treatment, the better is QOL. Despite this picture, it remains to be seen whether the same factors could influence the QOL in women from diverse cultural contexts, which may determine different perceptions of QOL.

The World Health Organization defines QOL “as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” [9]. There are various definitions of QOL. However, an analysis of these definitions suggests that QOL is a subjective construct, contemplating aspects of individual existence and experience. The study of QOL should focus on women’s self-evaluation. Therefore, QOL questionnaires were elaborated with the purpose of producing objective data

from subjective realities. The translation and validation of such questionnaires allowed uniformity of QOL investigation, as well as the comparison of results obtained from studying different populations. Lately, there has been an increase in the number of publications related to QOL in the health field. In this context, oncology was the specialty faced with the need to assess its patients' life conditions [10].

Overall, QOL studies in women with gynecologic cancer were conducted in developed countries [3-7], thus portraying a different reality than that experienced by women from developing countries. There is little data on the influence of pretreatment factors on these women's QOL. Considering these aspects and seeking to collaborate on understanding the repercussions of this cancer group on the lives of women, the current study was conducted to evaluate QOL in women with gynecologic cancer and identify its associated factors.

Methods

Subjects

Between March 2005 and March 2006, a cross-sectional study was conducted at the Women's Hospital, School of Medicine, Universidade Estadual de Campinas, Brazil. This institute is a public healthcare service, a referral center for the treatment of gynecologic cancer. Participants were selected among those who were consecutively referred to radiotherapy. Women with cervical or endometrial cancer, aged between 18 and 75 years who were undergoing the entire treatment at the institution were included. Women with a history of other types of cancer were excluded. Of 111 women, four had a history of breast cancer and four refused to participate in the study. Thus, 103 women were included.

The evaluation included an interview, clinical evaluation and complete blood count. Participants were interviewed to investigate the prevalence of symptoms (pain, vaginal bleeding, nausea and/or vomiting, hot flashes), clinical and sociodemographic characteristics, such as age, race/ethnicity, body mass index (BMI), school education, marital status, family income per month, menopausal status. Disease-related data were gathered from medical records: cancer site, surgery, cancer stage according to the International Federation of Gynecology and

Obstetrics (FIGO). Anemia was defined when the participant had a hemoglobin value lower then 11.0 g/dl. This study was approved by the Institutional Review Board and all women signed an informed consent form.

Quality of Life Assessment

To assess QOL a questionnaire of the World Health Organization's Quality of Life instrument-abbreviated version was used (WHOQOL-BREF) [11]. WHOQOL-BREF is a generic instrument for assessment of QOL, which has already been translated and validated to the Portuguese language in Brazil [12]. It is a multidimensional questionnaire, composed of 26 items, with four domains: physical, psychological, social relationships and environment. There are also two questions for assessment of overall QOL and general health. Higher scores indicate a better QOL.

Statistical analysis

The results were expressed in median, mean, standard deviation (SD) and minimum and maximum values, or absolute and relative frequencies, according to the type of variable. For data analysis, variables were categorized as follows: age (≤50, >50 years), race/ethnicity (white, non-white), education (≤4, >4 years), menopausal status (premenopause, postmenopause), employment status (employed, unemployed, homemaker), family income per month (≤484, >484), marital status (with or without a partner), cancer site (cervix, endometrium), stage (I/II, III/IV), BMI (≤27.8, >27.8Kg/m^2). Sexual activity, surgery for cancer treatment, anemia, current use of hormone therapy, pain, vaginal bleeding, nausea and/or vomiting and hot flashes were categorized in yes or no.

QOL scores were transformed in a 0 to 100 scale, and because of its asymmetrical distribution, were expressed in median. Bivariate analysis was performed applying the Mann-Whitney test. For multivariate analysis, variables with p value <0.15 were selected and the Structural Equation Models (SEM) [13] with multiple linear regression, calculation of estimated parameter (EP) and coefficient of determination (R^2) were used. In the investigation of possible factors associated with QOL, sociodemographic and clinical characteristics, as

well as cancer-related symptoms were consideredg independent variables, while QOL was considered a dependent variable. P ≤ 0.05 was considered statistically significant. For data analysis, the SAS program, version 8.2 and AMOS program, version 5.0 were used.

Results

The interview was conducted an average of 14.4 days before radiotherapy began. The mean (±SD) age of the participants was 56.8±11.6 years, and BMI was 27.8±6.2 Kg/m^2. The majority of participants reported having four years or less of school education (77.7%) and was postmenopausal (81.5%) and more than half reported living without a partner (50.5%). Other sociodemographic characteristics are presented on Table 1.

Table 2 shows clinical characteristics and prevalence of symptoms. The majority of participants had cervical cancer (65%), and at an advanced stage (63.1%). The most common complaints were pain (49.5%) and vaginal bleeding (36.9%). The prevalence of anemia was 22.3%. Sexual activity was reported by 15.5% of women.

QOL scores are presented in Table 3. The highest scores were observed in the social relationships domain and overall QOL, medians of 75, respectively, while the lowest scores were found in the environment domain and general health, medians of 62.5 and 50, respectively.

On bivariate analysis, it was observed that pain was associated with the lowest QOL scores in the physical (p=0.001) and environment (p=0.002) domains, and overall QOL (p=0.015) and general health (p=0.011). Women with cervical cancer (p=0.018), at an advanced stage (p=0.008) and premenopausal women (p=0.029) had lower QOL scores in general health. Other associations are presented in Table 4.

On multivariate analysis, pain was negatively associated with physical domain (EP: -0.40; p=0.001), overall QOL (EP: -0.21; p=0.024) and general health (EP: -0.22; p=0.013). Complaints of nausea and vomiting are negatively related to physical domain (EP: -0.14; p=0.010), while vaginal bleeding was

negatively associated with general health (EP: -0.16; p=0.047). The history of surgery positively affected general health (EP: 0.35; p=0.001) (Figure 1).

Discussion

The aim of the current study was to evaluate QOL and identify its associated factors in a cohort of women with gynecologic cancer prior to radiotherapy. Of the domains in the WHOQOL-BREF questionnaire, social relationships and physical domains had the best scores, while the environment domain had the lowest score. Among the factors related to QOL, cancer symptoms predominated. Pain, vaginal bleeding, anemia and nausea and/or vomiting negatively affected QOL, while the history of surgical cancer treatment was positively associated with QOL.

WHOQOL-BREF is a generic questionnaire with cross-cultural validity [14] which permits the comparison of QOL in patients with different diseases. There are no normative data of WHOQOL-BREF for the general population in Brazil. However, other authors, who assessed patients with chronic diseases such as systemic lupus erythematosus [15], rheumatoid arthritis [16], congenital heart defects [17], HIV/AIDS [18], leprosy [19], reported good QOL scores in the social relationships domain, in agreement with our findings.

A diagnosis of cancer mobilizes the family which provides support to the patient. Furthermore, in the institution where the study was conducted, women with gynecologic cancer received multidisciplinary care, highlighting psychosocial support. Family and psychosocial support contribute to minimize the impact of gynecologic cancer, not only in the social relationships domain, but also in the psychological domain. In this domain, positive and negative feelings, self-esteem, spirituality/ religion/personal beliefs are assessed. These aspects are closely related to the cultural context of the individual. Spirituality buffered the adverse effect of stress on adjustment [20], raising self-esteem and encouraging positive attitudes towards adverse events in life such as a diagnosis of cancer and other chronic diseases. Previous studies have described a relationship between spiritual coping, mood and QOL in cancer patients, indicating that the use of negative

spiritual coping was associated with the highest levels of anxiety [21], while spiritual support was related to better QOL scores [22].

In contrast to many QOL instruments, the WHOQOL-BREF questionnaire includes an environment domain, in which financial resources, transport, access to health services and new information are assessed, among other aspects. Therefore, the environment plays an important role in determining health status, limiting or facilitating access to these services [18]. This aspect may be relevant to developing countries where access to health care still has its limitations and flaws, as may be observed in the present study that included a large number of advanced-stage cancer cases. It is worth mentioning that the institution conducting this study is a public health service, managing women of low income and little education. Therefore, the financial difficulties of the socially disadvantaged may delay access to health services and information about the disease. This fact may have negatively influenced QOL. Other authors have described a similar picture [18].

Analysis of the physical domain in women with gynecologic cancer suggests that it was less affected than that of patients with other chronic conditions, such as rheumatic diseases [15, 16], leprosy [19], and congenital heart disease [17]. Cultural differences and severity of symptoms in these diseases are some factors that may explain the lesser impact of gynecologic cancer on the physical domain. Despite the possible differences in intensity of physical domain impairment, a common finding in studies of chronically ill patients is that physical domain is usually one of the most affected by the presence of symptoms [15-17], which is in agreement with our findings.

Cancer-related symptoms may be systemic, such as anemia, fatigue and weight loss, or localized, including pain and bleeding [23]. In the present study, the prevalence of anemia was 22.3%, which was lower than the 49.1% described in a previous study [24]. This difference is possibly due to the fact that only women who had not undergone chemotherapy and/or radiotherapy were evaluated in our case study. Although less frequently observed than in previous reports, anemia negatively affected the physical domain. Anemia may run its course with symptoms such as fatigue, dyspnea, palpitations, cardiovascular complications,

depression, nausea, cognitive dysfunction and impairment in sexual and immune function [25]. The European Cancer Anaemia Survey (ECAS) was one of the largest prospective and observational studies aimed at investigating different aspects of cancer-related anemia. This study was conducted in 24 European countries and more than 15,000 patients of both sexes, with different types of tumors (gynecologic, breast, lung, gastrointestinal, lymphoma, myeloma) were evaluated [26]. In the ECAS study, gynecologic cancer and the female sex were identified as risk factors for anemia [24].

In addition to toxicity due to antineoplastic therapy, women with gynecologic cancer have a higher risk of anemia due to the anatomic relations of the tumor. Tumor progression may lead to pelvic pain and vaginal bleeding [23]. Vaginal bleeding may negatively influence QOL, aggravating anemia or become a social embarrassment. Furthermore, it may be interpreted as worsening of the disease, impairing the woman's own perception of improvement in health status, which may partly explain its negative association with general health. Therefore, vaginal bleeding may directly influence QOL, affecting self-perception of general health, or indirectly compromising the physical domain, making it difficult to manage the clinical picture related to anemia. Other authors have reported an association between anemia, fatigue [27, 28] and worse performance status [24], with negative repercussions on QOL [27], consistent with that observed in the present cohort. Considering fatigue as the cardinal symptom of anemia and its relation with QOL [27], the control of hemoglobin levels may lead to a reduction in fatigue and improvement in functional capacity and consequently in QOL [29].

Another complication of tumor progression that may affect QOL is pain. The International Association for the Study of Pain defines pain "as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [30]. The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment. Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life [30]. In this context, pain has a multifactorial origin, and may affect all

QOL dimensions, including physical, social, psychological and spiritual components [31]. Other authors have observed a relationship between pain and depression in women with gynecologic cancer, reporting that women taking antidepressants had a lower chance of presenting major depression and referring pain [4]. These data suggest that there is an interrelationship between physical and psychological symptoms, indicating the need to adopt an integral approach to pain investigation and treatment, particularly in cancer-related pain. These data further indicate that the impact of pain is not limited to physical aspects, imposing restrictions on the performance of daily activities. However, its impact encompasses a woman's self-perception of health status and overall QOL in a complex manner. Therefore, pain treatment strategies need to consider not only the anatomic or pathophysiological aspects, but also the subjectivity present in its interpretation and its possible repercussions on QOL. In the context of gynecologic cancer, the best results in pain treatment may be achieved by a multidisciplinary team, composed of an oncogynecologist, clinical oncologist, radiotherapist, nurse, psychiatrist, pain specialist and nutritionist [23].

Among factors related to QOL, the impact of gastrointestinal symptoms, e.g. nausea and vomiting might be one of the least reported symptoms. Although nausea is a subjective symptom that is relatively neglected, its occurrence is associated with a lack of appetite causing possible weight loss and impairment in QOL [32]. Nausea and vomiting, in a manner similar to anemia, may contribute to the occurrence of fatigue, with a reduction in functional capacity. This picture is consistent with the relationship between these symptoms and a worse QOL observed in the present study. Advances were made in anti-emetic therapy, providing a satisfactory control of vomiting. However, complaints of nausea require greater attention of health professionals, since these symptoms are highly subjective, stressful [32] and difficult to treat. Adequate support for the control and prevention of these symptoms and their complications (weight loss, dehydration, water and electrolyte disorders) is warranted, since they may negatively affect QOL, as demonstrated.

The observed association between surgery and QOL is counter-intuitive. Despite morbidity due to surgery, it may be viewed as a possibility of cure,

explaining its relationship with QOL. However, this finding requires further investigation in studies specifically designed for this purpose.

Previous studies have shown the association of other factors with QOL, which tend to disappear in the long run [7, 33]. On bivariate analysis, diverse factors were negatively associated with QOL. But considering all variables in conjunction, only cancer symptoms negatively affected QOL. Confirming our findings, Wan et al. [34] observed that sociodemographic factors exert little influence on QOL in cancer patients when other variables are controlled.

For the interpretation of our data, it is worth keeping in mind several aspects. A generic QOL questionnaire was used. It may fail to assess specific domains that may affect QOL in women with gynecologic cancer, such as sexual functioning. However, this domain may also not be adequately measured by cancer-specific instruments [35]. Although the WHOQOL-BREF is a generic tool, it has permitted the identification of factors that negatively affect QOL in women with gynecologic cancer. To our knowledge, no site or cancer-specific tool has been translated and validated to the Portuguese language in Brazil, so its use has been precluded. Cross-sectional design did not permit the establishment of causality, but allowed the identification of associations.

In the current study, we emphasized the use of a standardized and internationally validated QOL questionnaire. This was possibly the first study conducted in Brazil to investigate factors associated with QOL in women with gynecologic cancer. Factors that negatively affected QOL were symptoms commonly referred by women with gynecologic cancer. It is necessary to provide adequate clinical and psychosocial support in an attempt to minimize the repercussions of these symptoms on QOL. The fact that anemia and complaints such as pain, vaginal bleeding, nausea and vomiting negatively affect QOL should draw the attention of health professionals involved in the care of these women, because these subjective complaints are undervalued at times.

In conclusion, cancer symptoms were factors that most interfered with QOL in women with gynecologic cancer. However, prospective studies are needed, using specific translated and validated instruments to enable the assessment of

aspects such as sexuality, performance status, pain, and anemia. Prospective evaluation will allow knowledge of whether the pretreatment factors that influence QOL will remain related to QOL in the long term.

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Table 1 – Sociodemographic characteristics in women with gynecologic cancer (n=103)

Characteristic	n (%)
Age (years)	
≤50	35 (34.0)
>50	68 (66.0)
Race/ethnicity	
White	54 (52.4)
Non-white	49 (47.6)
Body mass index (kg/m^2)	
≤27.8	53 (51.5)
>27.8	50 (48.5)
School education (years)	
≤4	80 (77.7)
>4	23 (22.3)
Employment status	
Employed	22 (21.4)
Unemployed	20 (19.4)
Homemaker	61 (59.2)
Marital status	
With partner	51 (49.5)
Without partner	52 (50.5)
Menopausal status	
Premenopause	19 (18.5)
Postmenopause	84 (81.5)
Current use of hormone therapy	
Yes	10 (9.7)
No	93 (90.3)
Family income per month (US$)	
≤484	50 (48.5)
>484	53 (51.5)

Table 2 – Clinical characteristics and prevalence of symptoms in women with gynecologic cancer (n=103)

Variables	n (%)
Cancer site	
Cervix	67 (65.0)
Endometrium	36 (35.0)
Stage	
I/II	38 (36.9)
III/IV	65 (63.1)
Surgery	
Yes	37 (35.9)
No	66 (64.1)
Anemia	
Yes	23 (22.3)
No	80 (77.7)
Pain	
Yes	51 (49.5)
No	52 (50.5)
Vaginal bleeding	
Yes	38 (36.9)
No	65 (63.1)
Hot flashes	
Yes	25 (24.3)
No	78 (75.7)
Nausea and vomiting	
Yes	11 (10.7)
No	92 (89.3)
Sexual activity	
Yes	16 (15.5)
No	87 (84.5)

Table 3 – Quality of life scores in women with gynecologic cancer (n=103)

WHOQOL-BREF	Median	Minimum	Maximum
Domains			
Physical	67.9	14.3	92.9
Psychological	66.7	25.0	95.8
Social relationships	75.0	41.7	100
Environment	62.5	31.3	90.6
Questions			
Overall quality of life	75.0	25.0	100
General health	50.0	0	100

Table 4 – Factors associated with quality of life in women with gynecologic cancer. Bivariate analysis (n=103)

WHOQOL-BREF		Median		Median	p-value*
Domains					
Physical					
Anemia	Yes	53.6	No	67.9	0.001
Pain	Yes	60.7	No	75.0	0.001
Environment					
Pain	Yes	59.4	No	65.6	0.002
Questions					
Overall quality of life					
Surgery	Yes	75.0	No	50.0	0.012
Pain	Yes	50.0	No	75.0	0.015
General health					
Cancer site	Cervix	50.0	Endometrium	75.0	0.018
Stage	I/II	75.0	III/IV	50.0	0.008
Surgery	Yes	75.0	No	50.0	0.001
Menopausal status	Premenopause	25.0	Posmenopause	75.0	0.029
Pain	Yes	50.0	No	75.0	0.011
Vaginal bleeding	Yes	50.0	No	75.0	0.001

*Mann-Whitney test.

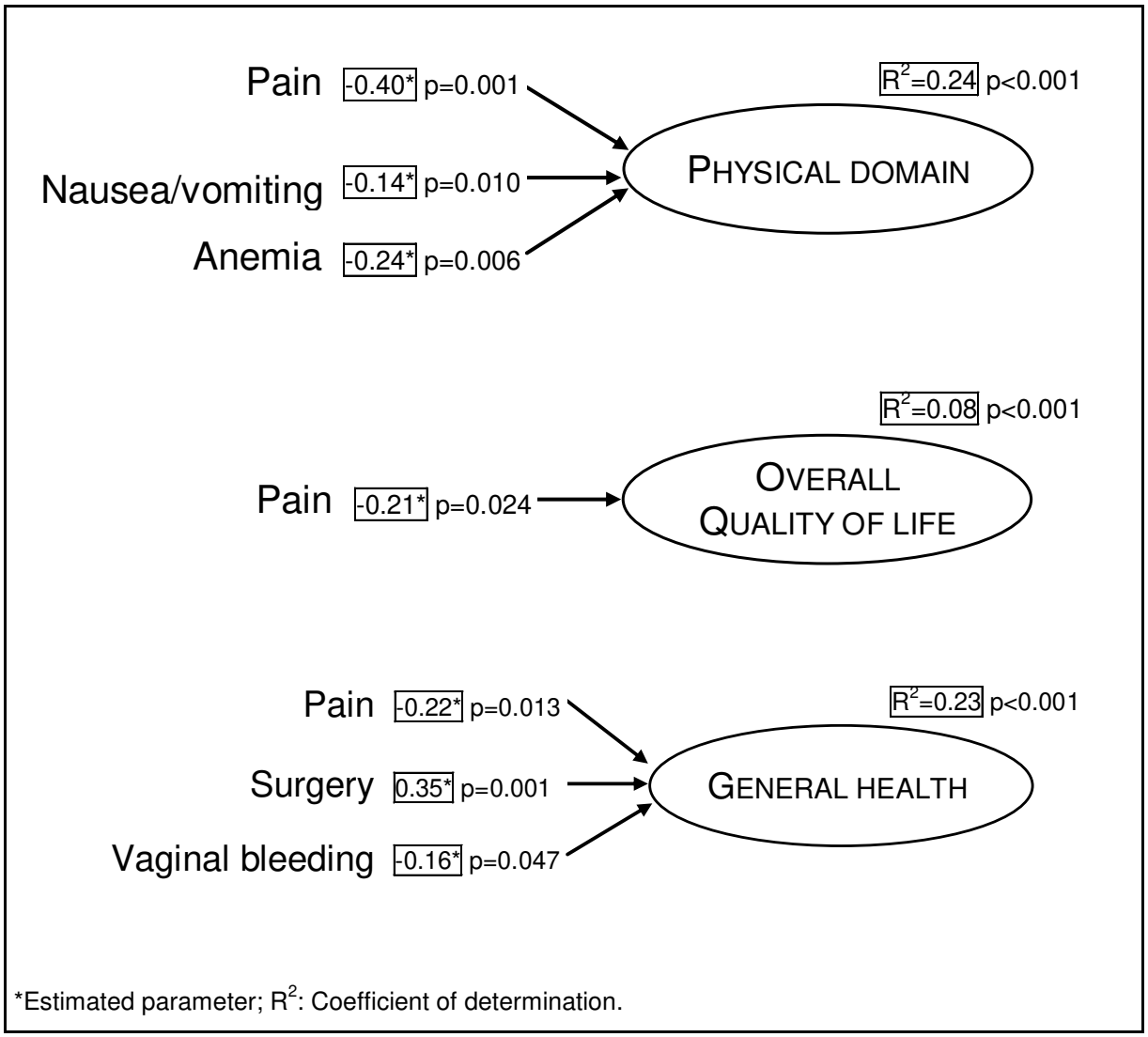

Figure 1 - Factors associated with quality of life in women with gynecologic cancer.

Multivariate analysis (n=103)

3.2. Artigo 2

Date: Oct 04, 2010
To: "Aarão Mendes Pinto-Neto" aarao@uincamp.br
From: "Menopause" dbarker1@partners.org
Subject: MENO Decision

Oct 04, 2010

RE: MENO-D-10-00233R1, entitled "Quality of Life, Menopause and Sexual Symptoms in Gynecologic Cancer Survivors: a cohort study"

Dear Dr. Pinto-Neto:

I am pleased to inform you that your manuscript has now been accepted for publication in Menopause - The Journal of The North American Menopause Society. All manuscript materials will be forwarded immediately to the production staff for placement in Volume 18.6 which is our June 2011 issue. Your manuscript will also appear on the Menopause web site in the Publish Ahead of Print section approximately 12-15 weeks from the date of acceptance after proofs have been finalized and approved.

The journal is adding to the Table of Contents a summary of each article. Because you know the material best, we ask that you respond to this email with 1-2 summary sentences about your article to be included on the table of contents page.

Thank you for submitting your interesting and important work to the journal.

http://meno.edmgr.com/

With Kind Regards,

Isaac Schiff, MD
Editor-in-Chief, Menopause
Menopause - The Journal of The North American Menopause Society

Quality of Life, Menopause and Sexual Symptoms in Gynecologic Cancer Survivors: a cohort study

Running title: QOL, menopausal symptoms and Gynecol. Cancer

Ana F. Vaz, Msc[1]: no conflict of interest
Aarão M. Pinto-Neto, MD, PhD[1]: no conflict of interest
Délio M. Conde, MD, PhD[2]: no conflict of interest
Lúcia Costa-Paiva, MD, PhD[1]: no conflict of interest
Sirlei S. Morais,Msc[1]: no conflict of interest
Adriana O. Pedro, MD, PhD[1]: no conflict of interest
Sérgio B. Esteves, MD, PhD[1]: no conflict of interest

[1]Department of Gynecology and Obstetrics, Universidade Estadual de Campinas, São Paulo, Brazil
[2]Breast Service, Hospital Materno Infantil de Goiânia, Goiás, Brazil

Funding source: none

Author for Correspondence: Aarão M. Pinto-Neto,MD,PhD, Department of Gynecology and Obstetrics, Universidade Estadual de Campinas. Rua Alexander Fleeming, 101, Cidade Universitária ‘‘Zeferino Vaz’’, 13083-970, Campinas, SP, Brazil.
Phone/Fax: +55 19 3521 9306; E-mail address: aarao@unicamp.br

Abstract

Objectives: To investigate the frequency of menopausal and sexual symptoms, proportion of sexually active women, assess and identify quality of life (QOL) predictors in gynecologic cancer survivors. **Methods:** A prospective case series following a cohort of radiation therapy patients with 107 women (aged 21- 75 years) with gynecologic cancer (cervical or endometrial cancer) who underwent radiotherapy pelvic in the Division of Radiotherapy in the Women's Integral Healthcare at the *Universidade Estadual de Campinas.* Side effects from radiotherapy were evaluated by the Common Terminology Criteria Adverse Event scale. QOL was measured by abbreviated version of the World Health Organization's Quality of Life instrument (WHOQOL-BREF) before (T0), and at 4 months (T1), 1 year (T2), and 3 years (T3) after radiotherapy. QOL scores were assessed over time by the Wilcoxon signed rank test. Multiple linear regression analysis was used to identify QOL predictors. **Results**: A decrease in the frequency of vaginal dryness (26.7% in T0 vs 8.3% in T3; $p<0.01$) and an increase in the proportion of sexually active women (21.5% in T0 vs 44.2% in T3; $p<0.01$) were observed. A significant increase in QOL scores was observed in the psychological domain and general health and overall QOL. Dyspareunia negatively affected the physical ($p<0.01$), psychological ($p<0.01$) and social relationships domains ($p<0.01$) and overall QOL ($p<0.01$) and general health ($p=0.04$). Family income was positively related to environment domain ($p<0.01$) and overall QOL ($p=0.04$) and general health ($p<0.01$). **Conclusions**: Data derived from this study indicated that gynecologic cancer survivors had a lower frequency of vaginal dryness and a higher proportion of these patients were sexually active three years after completion of radiotherapy. Furthermore, QOL improved and dyspareunia negatively affected various QOL dimensions.

Keywords: Gynecologic cancer, Quality of life, Menopause symptoms, Sexual function, Radiotherapy.

Introduction

Gynecologic malignancy is one of the most common groups of neoplasm and uterine cervical cancer is the second most common gynecologic malignancy worldwide.[1] Furthermore, there is a twofold increase in the incidence of gynecologic cancer in developing countries.[2] An estimated 18,430 new cases of uterine cervical cancer were predicted for 2010 in Brazil, where it is the third most common malignancy among women.[2] In contrast, endometrial cancer is more common in developed countries, where it ranks fourth among malignant tumors in women[1,3].

For management of gynecologic cancer, the 3 major treatment modalities used are surgery, radiotherapy and chemotherapy[4]. Given that radiotherapy is associated with impairment in quality of life (QOL)[4-7] and the 5-year survival rate in patients with uterine cervical cancer and endometrial cancer is considered relatively good, QOL assessment in these women has become imperative.[8] Studies that prospectively assessed QOL in women with gynecologic cancer have described impaired QOL during and after completion of radiotherapy, with improvement after treatment[9-12].

Pelvic radiotherapy may be associated with late adverse effects such as ovarian failure, dyspareunia, vaginal dryness, a decrease in vaginal elasticity, stenosis and foreshortening of the vagina.[13-16] These vaginal effects may interfere in sexual functioning of gynecologic cancer survivors,[13,15-18] causing considerable distress.[17]

Previous studies have reported a significant increase in complaints of dyspareunia after pelvic radiotherapy[13,19] and have described that cervical cancer survivors treated with radiotherapy had poorer sexual functioning and significantly worse health-related QOL than did those treated with surgery.[18] According to some authors, sociodemographic characteristics exert limited influence on the QOL of cancer patients when other variables are taken into account.[20] Sociodemographic variables such as income, age, school education and race were not associated with QOL in women with gynecologic cancer before[21] and after treatment[8]. However, the relationship between these factors and QOL has not been prospectively evaluated.

Although some studies have investigated QOL and sexual function of gynecologic cancer survivors,[7,18,22] the frequency and influence of menopause

and sexual symptoms on QOL in gynecologic cancer patients after radiotherapy has been poorly documented. We conducted the current study to prospectively investigate the frequency of menopausal and sexual symptoms, the proportion of sexually active women, in addition to assessing and identifying QOL predictors in gynecologic cancer survivors.

Methods

Participants

A prospective case series following a cohort of radiation therapy patients was conducted from March 2005 to March 2009 in the Women's Integrated Healthcare Center, Campinas State University School of Medicine, in Campinas, Brazil. Participant selection has been previously described in detail.[23] Briefly, women with gynecologic cancer, aged between 21 and 75 years were included in the study. Women with a previous history of pelvic radiation were ineligible. Of the 111 women selected, four refused to participate in the study due to lack of time. Therefore, 107 women were included in the study and only 101 completed radiation therapy.

During the follow-up period, tumor recurrence, death and patients lost to follow-up were reasons for exclusion. Thus, 81 women returned for a follow-up visit at four months (13 were lost to follow-up, 01 died, and 06 were absent), 69 returned at one year (10 tumor recurrences, 01 died, 05 were lost to follow-up, and 02 were absent), and 53 returned at three years (09 tumor recurrences, 04 deaths, 04 were lost to follow-up and 01 was absent) after completion of radiation therapy (Figure-1). Women who missed the follow-up visit were not excluded from the study. The women were not stratified by stage and cancer type, treatment modalities and age because although this study had a larger sample size than some similar studies, the sample is still too small for this type of analysis.

Patient assessment before radiotherapy included an interview and clinical evaluation. Participants were interviewed to investigate social demographic and clinical characteristics, e.g. age, race/ethnicity, level of education, marital status, sexual activity, monthly family income, employment status and menopausal status. Disease- and treatment-related data collected from medical records were

cancer site, surgery, chemotherapy, cancer stage according to the International Federation of Gynecology and Obstetrics (FIGO). The radiotherapy procedure was previously described in detail.[23]This study was approved by the Institutional Review Board and all women signed an informed consent form.

Sexual activity, menopause and sexual symptoms

The frequency of menopausal and sexual symptoms was investigated according to the Common Terminology Criteria Adverse Event Scale (CTCAE) v 3.0, a comprehensive grading system for the adverse effects of cancer treatment that contains a section for assessment of menopausal and sexual symptoms. The occurrence of dyspareunia, vaginal dryness, and hot flashes was assessed prospectively by one of the researchers at four points in time (T): in the first medical consultation in the Radiotherapy Division before starting radiotherapy (T0), at 4 months (T1), at one year (T2) and at three years (T3) during follow-up visits after completion of radiotherapy. A decrease in sexual interest was evaluated in T1, T2 and T3. The proportion of sexually active women was prospectively assessed at four time points.

Quality of Life Assessment

For QOL assessment, a questionnaire of the abbreviated version of the World Health Organization's Quality of Life instrument was used (WHOQOL-BREF).[25] WHOQOL-BREF is a generic quality of life scale developed for QOL assessment. The Brazilian Portuguese version of the WHOQOL-BREF has already been translated and validated.[26] It is a multidimensional questionnaire composed of 26 items, measuring four domains: physical, psychological, social relationships and environment. There are also two questions for overall QOL and general health assessment. Higher scores indicate a better QOL. QOL was assessed prospectively by one of the researchers in the following four points in time (T): in first medical consultation at the Radiotherapy Division before starting radiotherapy (T0), and at 4 months (T1), 1 year (T2), and 3 years (T3) during follow-up visits after finishing radiotherapy. QOL was studied using the patients as their own controls over time.

Interventions and suggestions for menopause and sexual symptoms

The standard interventions and suggestions for sexual activity, menopause and sexual symptoms were offered to all these women. Some suggestions made concerned radiotherapy effects on the pelvic region (menopause and vaginal effects such as stenosis, decreased lubrication, dyspareunia). The use of a vaginal dilator was recommended twice daily for 2 years when starting brachytherapy. A vaginal lubricant was prescribed for complaints of dyspareunia and vaginal dryness. Patients were referred to a menopause outpatient clinic for complaints of vasomotor and sexual symptoms (decreased libido, dyspareunia and hot flashes). Acceptance of the suggestions and interventions was not evaluated. As a result, it was not possible to determine their interference in sexual activity, menopause and sexual symptoms in these women.

Statistical analysis

Results were presented as medians, means and standard deviations (SD) or as absolute and relative frequencies, according to the type of variable. For QOL assessment, only women who completed all four evaluations were taken into consideration.

QOL scores did not have a normal distribution and were evaluated over time using a non-parametric Anova for repeated measures (Friedman). The Wilcoxon signed rank test (if significant) was also used to compare each time in relation to baseline value. Bivariate analysis was used to identify QOL predictors by the Mann-Whitney test. The McNemar test was used to evaluate differences between the frequency of menopausal and sexual symptoms at different time periods. For multivariate analyses, variables with $p<0.15$ were selected and Structural Equation Models[27] with multiple linear regression analysis, calculation of estimated parameter (EP) and coefficient of determination (R^2) were used. To investigate QOL predictors, sociodemographic and clinical characteristics, sexual activity, menopause and sexual symptoms were considered independent variables, while the domains and two questions related to overall QOL and general health from the WHOQOL-BREF questionnaire were considered dependent variables. Statistical significance

level was set at $p< 0.05$. For data analysis, the SAS[28] program, version 8.2 and AMOS program, version 5.0 were used. The AMOS program used the SEM (Structural Equation Model) to perform multivariate analysis.

Results

Sociodemographic and clinical characteristics of the participants are shown in Table1. The median age of the participants before radiotherapy was 60 years (range: 21-75 years). The majority of patients (63.5%) were shown to have cervical cancer and advanced stages of disease (III-IV), 75.7% reported a monthly family income of US$ 484.00 or lower and 77.6% had four or less years of school education. Almost half of the participants referred living with a partner (50.5%). A smaller proportion of women had undergone surgery (37.4%) used HT (11.2%) and had received chemotherapy (17.8%). Vaginal bleeding and pain were reported in 35.5 % and 48.6% of women, respectively.

Eighty-nine women (83.2%) received external pelvic radiotherapy and brachytherapy. Eight women received only external pelvic radiotherapy and 10 women received only brachytherapy. At the end of 03 years, 49.6% of these women were excluded from the study: 19 (17.7%) due to tumor recurrence, 10 (9.5%) died and 24(22.4) were lost to follow-up. After radiotherapy, 45.9% of the women experienced dyspareunia, 44.4% had hot flashes, 29.7% described a decrease in sexual interest and 24.3% had vaginal dryness during the three-year period. The percentage of sexually active women during this period was 45.7% (Data was not shown in a table).

Table 2 showed a significant increase in the proportion of sexually active women after radiotherapy compared to that before radiotherapy. There was also a significant increase in the frequency of dyspareunia in T1 (33.3%; $p<0.01$), which was maintained in T2 (33.3%; $p<0.01$). Vaginal dryness (33.3%; $p=0.03$) and hot flashes (37%; $p=0.03$) increased in T1. Vaginal dryness decreased in frequency in T2 (0; $p<0.01$) and T3 (8.3%; $p<0.01$).

QOL scores are presented in Table 3. In comparison to scores before radiotherapy, QOL scores increased significantly in the following domains: physical in

T1 (75.0±15.7; p<0.01), psychological in T1 (71.5±14.0; p<0.01), T2 (71.6±12.4; p=0.01) and T3 (70.4±14.4; p<0.01); as well as overall QOL in T1 (76.1±16.1; p<0.01) and T3 (77.8±20.3;p=0.01). QOL scores increased in general health at all time periods: T1 (77.3±20.0; p<0.01), T2 (77.3±16.0; p<0.01), and T3 (74.4±19.8; p=0.02).

On bivariate analysis, dyspareunia was negatively associated with physical (p=0.04), social relationship (p=0.02) and psychological domains (p=0.03) in T3, and overall QOL in T2 (p=0.03). Being sexually active was negatively related to the social relationship domain in T3 (p=0.02) and decreased sexual interest negatively affected overall QOL in T2 (p=0.04) (Table 4).

Table 5 shows the factors associated with QOL at three years after completion of radiotherapy on multivariate analysis. Dyspareunia was negatively associated with the following domains: physical (EP:-19.09; p=0.001), psychological (EP:-17.84; p=0.001), and social relationship (EP:-14.28; p=0.002), as well as overall QOL (EP:-16.88; p=0.014) and general health (EP: -13.70; p=0.047). Higher family income was positively related to environment domain (EP: 0.011; p=0.001), overall QOL (EP: 0.009; p=0.040) and general health (EP: 0.011; p=0.009).

Discussion

The aim of this prospective case series following a cohort of radiation therapy patients was to investigate the frequency of menopausal and sexual symptoms, the proportion of sexually active women, as well as to assess and identify QOL predictors in gynecologic cancer survivors. A significant increase in the proportion of sexually active women and a decrease in the complaint of vaginal dryness were observed. Furthermore, there was an improvement in QOL, which had been adversely affected in various dimensions due to the occurrence of dyspareunia.

A significant increase in the proportion of sexually active women (from 21.5% to 44.2% after three years), in comparison to those at the initial evaluation, indicates impairment in sexual functioning before undergoing radiotherapy. The reason for this sexual impairment before starting radiotherapy may have been related to cancer diagnosis, surgery (37.4%) and cancer-related symptoms such as pain (48.6%) and vaginal bleeding (35.5%). In the following evaluations, a significant

increase in the proportion of sexually active women could be explained by improvement in symptoms due to treatment and control of the disease. According to Stead[29], sexual function in women with gynecologic cancer may be impaired by symptoms such as vaginal discharge, pain and bleeding. In agreement with our data, it has been reported that 15% of the women with endometrial cancer were sexually active before radiotherapy and a year after treatment this proportion rose to 39%.[30] Other authors described a decrease in the percentage of sexually active women after radiotherapy,[15] where only 63% of these women continued to be sexually active a year after treatment. This may have been related to a retrospective initial evaluation, even though the majority of participants had early-stage tumors (I/II).

The frequency of symptoms after radiotherapy was assessed: dyspareunia (45.9%), hot flashes (44.4%), decrease in sexual interest (29.7%) and vaginal dryness (24.3%). In agreement with our results, dyspareunia was observed in 43% of cervical cancer patients[13] and in 40% of gynecologic cancer patients[31] after treatment. A higher frequency of dyspareunia (55%) was observed in a study[15] that included cervical cancer patients at a two-year follow-up visit after radiotherapy. The reason may be the higher proportion of sexually active women in that study. Dyspareunia was the most common symptom that increased significantly until one year after completion of radiotherapy, according to our results. Other studies also reported an increase in this symptom after radiotherapy.[13,19]

A significant increase in hot flashes was observed only in T1 (24% vs 37%), with a decrease in subsequent evaluations, although there was no statistical significance. A decrease in hot flashes after one year of treatment is not explained by HT use, since only 1.2 % of women were using HT. It may have been related to a shorter duration of hot flashes in patients with gynecologic cancer. Further studies are required with a larger number of patients, using specific instruments to confirm these data.

Other researchers observed lower rates of hot flashes that range from 6%[32] to 31.4%[33] in gynecologic cancer patients after receiving different treatment modalities. These differences may be explained by the cross-sectional study design and the inclusion of women treated for at least two years. Other investigators

reported similar rates of vaginal dryness: 21.6%[32]and 24.3%[17] in uterine cervical cancer patients treated with surgery or radiotherapy. In contrast, Jensen et al[15] reported that 35% of the patients had a moderate or severe decrease in vaginal lubrication after radiotherapy. However, a significant decrease in vaginal dryness was observed in the current study, at three years after completion of radiotherapy (8.3%) compared to the first evaluation after radiotherapy (26.7%). The reason for this decrease may be the use of vaginal lubricants by 40.5% of the women following the first return visit after radiotherapy, as routinely recommended by this institution.

In agreement with our data, Wenzel et al[33] observed that 28.6% of gynecologic cancer survivors had lost interest in sexual activities after undergoing various treatment modalities. In contrast, 65% of women with gynecologic cancer treated with chemotherapy or radiotherapy reported a decrease in sexual desire since the time of cancer diagnosis.[31]The difference in results may have occurred because we only considered decreased sexual interest due to radiotherapy in our study. Lower proportions of sexually active women were also observed in the current study.

Before radiotherapy, 82.2% of women were postmenopausal and 11.2% used HT. After treatment, all women were menopausal and the use of HT decreased from 1.2%, to 2.9% to 5.7% (at 4 months, 1 year and 3 years after radiotherapy). Thus, due to the low prevalence of HT use, we could infer that HT did not interfere in the frequency of sexual activity, menopausal and sexual symptoms in these women.

Despite the menopausal and sexual symptoms, QOL improved after radiotherapy at all time points evaluated (T1 to T3) compared to the initial evaluation (T0). Studies prospectively assessing QOL in gynecologic cancer patient after treatment[9,10,12,34] reported an improvement in QOL and confirmed our findings. At the three-year follow-up visit after radiotherapy, there was a significant improvement in QOL scores on the psychological domain and on two questions related to overall QOL and general health.

Previous studies reported impairment of emotional functioning at the initial evaluation of gynecologic cancer patients with improvement in QOL after treatment[9,10,34]. In a study by Lutgendorf et al,[34] QOL improved in gynecologic

cancer patients one year following treatment, compared to the initial evaluation. Bye et al[9] observed that overall QOL improved in gynecologic cancer patients following radiotherapy and their result was in line with our data.

In the present study, general health was most adversely affected at the initial assessment, with a significant increase in scores at the remaining time points evaluated (T1 to T3). Since this question evaluated a subjective impression of a woman concerning her health, it is possible that early diagnosis, surgery and cancer-related symptoms may have negatively interfered in the perception of health before radiotherapy. According to previous studies,[21] general health was more adversely affected before radiotherapy in gynecologic cancer survivors and was negatively associated with cancer-related symptoms such as pain and vaginal bleeding. After radiotherapy, disease control with consequent improvement in symptoms, and emotional support offered by the institution may have contributed to a positive perception of health. As a result, general health improved significantly in the following time period.

Bivariate analysis showed that after radiotherapy, dyspareunia was significantly associated with a poorer QOL on the following domains: physical, social relationships, psychological and for the question of overall QOL. It was also observed that sexually active women and those with decreased sexual interest had lower scores in the social relationship domain and overall QOL, respectively. Greimel et al[7] also observed a significant deterioration in QOL in cervical cancer patients treated with surgery and radiotherapy on various functioning scales (physical health, role emotional, cognitive and social functioning), in comparison to the remaining groups (control and surgery/chemotherapy) where urogenital and vaginal symptoms were significantly more frequent. In 2006, Bradley et al[8] reported a poorer overall QOL in women with gynecologic cancer (cervix and endometrium) who had persistent side effects after different treatment modalities. In agreement with those authors, our data showed a worse overall QOL in women who experienced dyspareunia and had decreased sexual interest. Other studies described an inverse correlation between symptoms and QOL.[10,21,35]

Dyspareunia and family income were the QOL predictors at the end of the study period. Dyspareunia, as expected, was the most common symptom following radiotherapy. This may have contributed to the negative interference of this symptom on the following domains: physical, psychological, environment and social relationship, as well as overall QOL and general health at three years after radiotherapy. Previous studies also reported a negative association between dyspareunia and QOL (mental component)[36] and a significant correlation between nervousness, depression and dyspareunia in middle-aged Brazilian women, where dyspareunia was experienced by 39.5% of the participants.[37] In 2007, Park et al[22] observed an association between dyspareunia and QOL (global health status; role emotional and social functioning) in cervical cancer patients following different treatment modalities. However, these authors failed to report whether the association was negative or positive and data were not shown in a table.

In contrast to many QOL instruments, the WHOQOL-BREF questionnaire includes an environment domain, in which financial resources, transport, access to health services and new information are assessed.[21]The environment plays an important role in determining health status, restricting or facilitating access to health services.[38] Family income was positively related to environment domain, overall QOL and general health at three years after completion of radiotherapy. It is worth mentioning that the present study was conducted in a public health service. In this context, difficulties in accessing healthcare services, financial problems, delay in the diagnosis and treatment, may have contributed to deterioration in QOL. In contrast, an increase in family income contributed to a positive perception of QOL, since it may have minimized the barriers to information, transportation and treatment.

For data interpretation, some aspects must be considered. A decrease in sample size caused by patient exclusion (due to tumor recurrence, death and loss to follow-up) was a limiting factor, albeit expected. A reduction of 48.3%[39], 22.6%[11] and 39.1%[12] in sample size was observed in studies where the ratio of stage III/IV disease was 30.4% to 41.5% and the period evaluated was 2 to 3 years. Therefore, we believe that 50% information at the end of the study period enabled us to make an inference, since a decrease in sample size was expected and the

proportion of women with stage III/IV disease was higher than that in other studies (63.5%). Sample size was small for the number of variables considered. Even with the statistical test performed that allowed the use of a smaller sample for this type of analysis, further studies are needed including a larger number of participants to confirm the results observed. The sample was not stratified by stage and cancer type, age and treatment modalities. This was also considered a limiting factor in this study. Nevertheless, in clinical terms we believe that this fact had little influence on final outcome. According to previous studies, cancer stage[8,11], and cancer type[10] were not associated with QOL in women with gynecologic cancer. Thus, a larger proportion of women with uterine cervical cancer (63.5%) would not alter the results relating to QOL, sexual activity, menopause and sexual symptoms. It is worth mentioning that previous studies have reported a poorer QOL[5,7] and higher frequency of menopause and sexual symptoms[18] for women treated with radiotherapy compared to those treated with surgery or chemotherapy. We also did not evaluate the impact of age on sexual functioning because sample size was too small for this type of analysis. However, we do know that greater age is associated with decreased sexual activity.[37] The lack of data relative to sexual activity, menopause and sexual symptoms before cancer diagnosis is a limiting factor in this study as well as in the majority of studies assessing sexual function in women with gynecologic cancer.[7,18] However, when entering the Radiotherapy Division, all women had already received a diagnosis of cancer and 37.4% had undergone surgery for cancer treatment. Since we do not have a centralized national database, information about sexual activity was lacking. Another limitation of the study was that the partner and availability for sexual relations were not evaluated. We only assessed if the woman had a partner. If she was sexually active, we asked if she had any problem during sexual intercourse. Another question was about the use of a vaginal lubricant and HT.

It is worth mentioning that the WHOQOL-BREF questionnaire is a generic instrument for QOL assessment. Nevertheless, when the study was initiated, we had no knowledge of a specific instrument that had been translated and validated into Brazilian Portuguese. That is the reason why we used the Common Terminology

Criteria Adverse Event Scale (CTCAE) v 3.0 to evaluate sexual activity, menopause and sexual symptoms. The CTCAE is a comprehensive grading system for the adverse effects of cancer treatment; it contains a section that assesses menopausal and sexual symptoms. Regarding cancer patients, we believe that a generic instrument would provide better assessment of QOL, despite its limitations. In addition to menopause issues, these women have a severe disease which may affect QOL even more than climacteric symptoms.

Concerning sexual symptoms (sexual functioning), the Common Terminology Criteria Adverse Event Scale (CTCAE) v 3.0 was used. It is a comprehensive grading system for the adverse effects of cancer treatment, containing a section for evaluation of menopausal and sexual symptoms. Since the (CTCAE) scale v 3.0 does not evaluate psychological symptoms related to menopause, it was not possible to assess the relationship between these symptoms and sexual function in these women.

Finally, despite its limitations this study was probably the first to evaluate a higher proportion of women with advanced gynecologic cancer (III/IV) for a 3-year period and the interference of sexual activity, menopause and sexual symptoms on the QOL of these women. Its major contributions are to show that changes in QOL over time do not differ from studies including a larger proportion of women with early- stage tumors (I/II), [9-12]i.e. QOL improves after treatment. It also identified sexual activity, menopause and sexual symptoms associated with QOL; showing the limitations inherent in this type of study and its implications for data analysis.

In the present study, we emphasized the use of a standardized and internationally validated QOL questionnaire, as well as the widely used Common Terminology Criteria Adverse Event Scale (CTCAE) v 3.0. A longitudinal study permitted a more accurate evaluation of the frequency of menopausal and sexual symptoms after radiotherapy that is usually underreported. The importance of investigating the frequency of these symptoms is based on various aspects. Understanding the frequency and duration of symptoms, as well as their interference in QOL allows us to offer adequate clinical care and psychological support to these women in an attempt to minimize repercussions on QOL. This may

be the first study in Brazil to prospectively evaluate the impact of menopause and sexual symptoms on the QOL of women with gynecologic cancer after radiotherapy.

Conclusion

In conclusion, we believe that these results are of interest to healthcare professionals involved in the management of gynecologic cancer patients. Although QOL improved in these women after completion of treatment and the number of sexually active women increased three years after radiotherapy, dyspareunia negatively affected various QOL dimensions. Further prospective studies with application of specific and generic QOL instruments to evaluate sexual function should be undertaken.

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Figure 1: Participant Flow-up Diagram

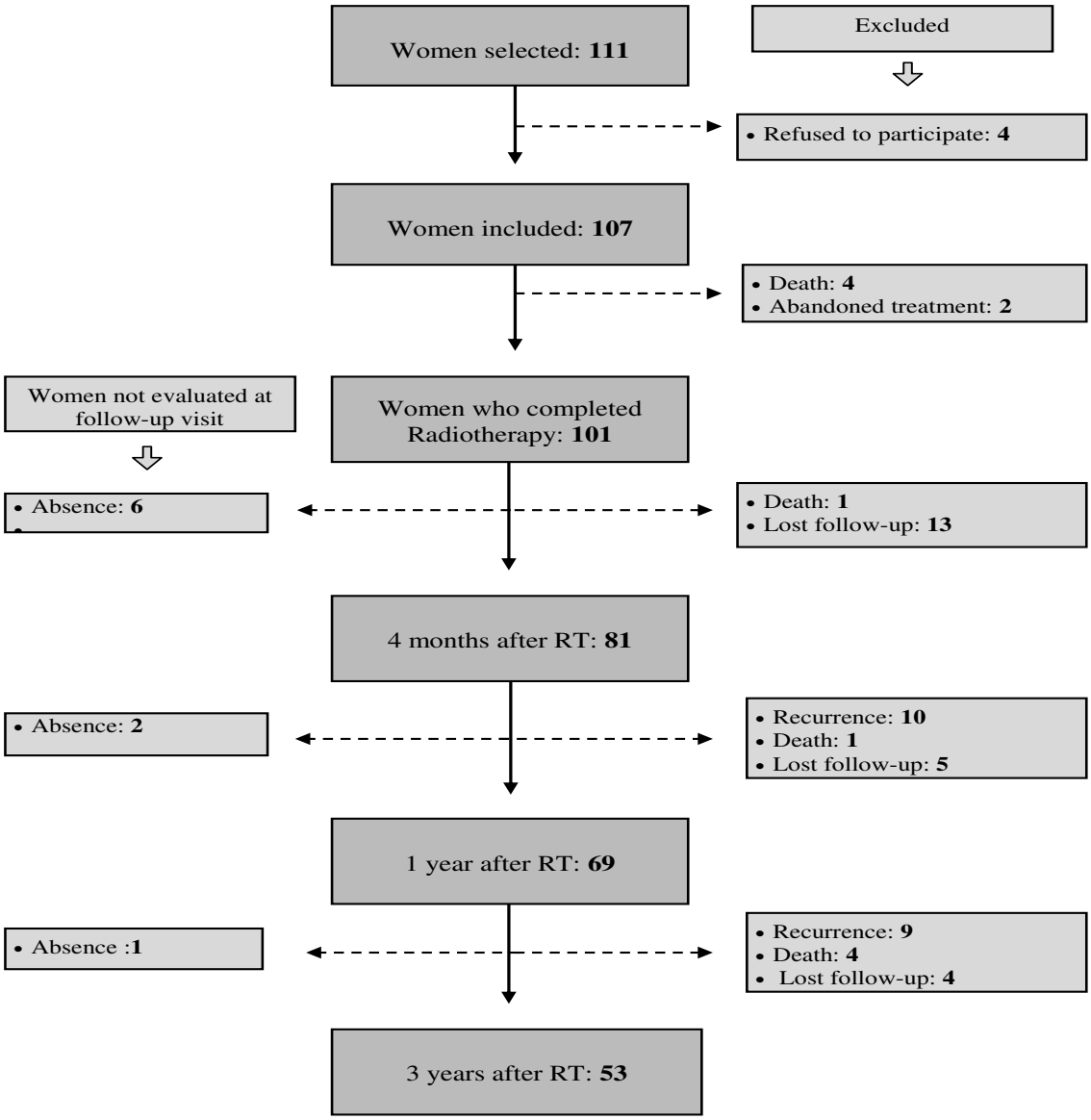

Table 1 – Sociodemographic and clinical characteristics of women with gynecologic cancer (N=107)

Characteristic	n (%)
Age (years)	
≤60	55 (51.4)
>60	52 (48.6)
Cancer site	
Cervix	68 (63.5)
Endometrium	39 (36.5)
FIGO Stage	
I/II	39 (36.5)
III/IV	68 (63.5)
Race/ethnicity	
White	49 (45.8)
Non-white	58 (54.2)
Education (years)	
≤4	83 (77.6)
>4	24 (22.4)
Marital status	
Without a partner	53 (49.5)
With a partner	54 (50.5)
Family income per month (US$)	
≤484	81 (75.7)
>484	26 (24.3)
Employment status	
Employed	22 (20.6)
Unemployed	22 (20.6)
Homemaker	63 (58.8)
Menopausal status	
Premenopause	19 (17.8)
Postmenopause	88 (82.2)
Current use of hormone therapy	
Yes	12 (11.2)
No	95 (88.8)
Surgery	
Yes	40 (37.4)
No	67 (62.6)
Chemotherapy	
Yes	19 (17.8)
No	88 (82.2)
Vaginal bleeding	
Yes	38 (35.5)
No	69 (64.5)
Pain	
Yes	52 (48.6)
No	55 (51.4)

Table 2. Sexual activity, menopause and sexual symptoms in gynecologic cancer survivors before (T0) and at 4 months (T1), 1 year (T2), and 3 years (T3) after radiotherapy. A comparison between frequency of symptoms at baseline and other time periods evaluated.

Variables	T0 (N=107)	T1xT0 (N=81)		T2xT0 (N=69)		T3xT0 (N=53)	
	%	%	p-value	%	p-value	%	p-value
Sexual activity			0.0010		0.0001		0.0039
Yes	21.5	39.2		46.3		44.2	
No	78.5	60.8		53.7		55.8	
Dyspareunia			0.0196		0.0196		0.1573
Yes	20.0	33.3		33.3		50.0	
No	80.0	66.7		66.7		50.0	
Vaginal dryness			0.0339		0.0016		0.0047
Yes	26.7	33.3		0		8.3	
No	73.3	66.7		100.0		91.7	
Hot flashes			0.0330		0.8185		0.7630
Yes	24.0	37.0		27.5		20.8	
No	75.3	63.0		72.5		79.2	
Decrease in sexual interest			-		0.7055		0.3173
Yes	-	23.1		26.9		21.1	
No	-	76.9		73.1		78.9	

McNemar test. Only women returning for a follow-up visit at each time period (T1, T2 or T3) were included in this analysis.

Table 3. Quality of life scores in gynecologic cancer survivors before (T0) and at 4 months (T1), 1 year (T2), and 3 years (T3) after radiotherapy.(N=44)

Domains	T0	T1xT0		T2 xT0		T3 xT0	
	Mean (SD)	Mean (SD)	p-value*	Mean (SD)	p-value*	Mean (SD)	p-value*
Physical	68.0 (17.0)	75.0 (15.7)	0.0087	71.5 (17.6)	0.2398	71.9 (16.8)	0.1063
Psychological	65.8 (14.9)	71.5 (14.0)	0.0073	71.6 (12.4)	0.0100	70.4 (14.4)	0.0070
Social relationship	79.1 (12.4)	81.9 (10.3)	0.1913	81.9 (12.7)	0.2121	81.2 (14.3)	0.4648
Environment	63.8 (11.8)	65.8 (10.6)	0.2583	67.9 (12.8)	0.0560	67.5 (12.6)	0.0942
Overall QOL	67.1 (17.7)	76.1 (16.1)	0.0049	73.3 (18.2)	0.0874	77.8 (20.3)	0.0120
General health	63.6 (20.5)	77.3 (20.0)	0.0002	77.3 (16.0)	0.0003	74.4 (19.8)	0.0204

Time effect by Friedman Anova for Repeated Measures $p < 0.05$ for all domains.*Wilcoxon signed rank test.

Table 4. Factors associated with quality of life in gynecologic cancer survivors according to time after radiotherapy. Bivariate analysis.

Variables	T1(N=81)		T2 (N=69)		T3 (N=53)	
	Mean (SD)	p-value	Mean (SD)	p-value	Mean (SD)	p-value
Physical						
Dyspareunia		0.7890		0.2122		0.0497
Yes	73.7 (12.9)		61.9 (20.1)		62.5 (19.2)	
No	72.5 (12.7)		71.3 (15.2)		77.1 (10.2)	
Social relationship						
Dyspareunia		0.3307		0.0512		0.0231
Yes	83.3 (12.4)		68.5 (16.0)		65.6 (16.9)	
No	79.8 (10.1)		81.4 (13.6)		80.6 (9.8)	
Sexual activity		1.0000		0.1371		0.0279
Yes	81.1 (10.9)		77.7 (15.3)		75.4 (14.3)	
No	80.4 (13.5)		83.5 (12.9)		84.6 (13.8)	
Psychological						
Dyspareunia		0.5326		0.2037		0.0369
Yes	74.2 (9.1)		65.3 (16.1)		64.1 (11.8)	
No	74.0 (10.2)		73.5 (12.6)		76.1 (6.0)	
Overall QOL						
Dyspareunia		0.8043		0.0376		0.0969
Yes	77.3 (17.5)		63.9 (18.2)		68.8 (25.9)	
No	75.0 (16.2)		79.6 (14.7)		86.7 (12.9)	
Decrease in sexual interest		0.8102		0.0445		0.1236
Yes	75.0 (15.8)		65.6 (12.9)		68.8 (12.5)	
No	76.0 (16.9)		78.3 (17.4)		82.9 (20.5)	

Mann-Whitney test

Table 5. Factors associated with quality of life in gynecologic cancer survivors three years after radiotherapy. Multivariate analysis. (N=53)

Domains	Variables	Estimated parameter	p-value	R2	p-value
Physical	Dyspareunia	-19.09	0.001	0.382	<0.001
Psychological	Dyspareunia	-17.84	0.001	0.540	<0.001
Environment	Family income	0.011	0.001	0.408	<0.002
Social relationships	Dyspareunia	-14.28	0.002	0.390	<0.016
Overall QOL	Dyspareunia Family income	-16.88 0.009	0.014 0.040	0.279	<0.001
General health	Dyspareunia Family income	-13.70 0.011	0.047 0.009	0.260	<0.001

R2: coefficient of determination. Variables considered in the analysis: age, cancer site, cancer stage, family income, race/ethnicity, school education, hot flashes, dyspareunia, decrease in sexual interest, sexual activity and vaginal dryness.

3.3. Artigo 3

----- Original Message ----- From: "Paula Sonneveld (ARCH)"
<paula.sonneveld@springer.com>
To: "aarao Mendes pinto-neto" <aarao@unicamp.br>
Sent: Wednesday, March 09, 2011 12:50 PM
Subject: Your Submission ARCH-11-3525R1

Dear Pinto-neto,

We are pleased to inform you that your manuscript, "QUALITY OF LIFE AND ADVERSE EVENTS AFTER RADIOTHERAPY IN GYNECOLOGIC CANCER SURVIVORS: A COHORT STUDY", has been accepted for publication in Archives of Gynecology and Obstetrics.

Please remember to quote the manuscript number, ARCH-11-3525R1 , whenever inquiring about your manuscript.

With best regards,
Klaus Diedrich

QUALITY OF LIFE AND ADVERSE EVENTS AFTER RADIOTHERAPY IN GYNECOLOGIC CANCER SURVIVORS: A COHORT STUDY

Ana Francisca Vaz[1], Délio Marques Conde, MD, PhD[2],Lúcia Costa-Paiva, MD, PhD[1], Sirlei Siani Morais[1], Sérgio Barros Esteves MD[1] Aarão Mendes Pinto-Neto, MD, PhD[1]

[1]Department of Gynecology and Obstetrics, [2]Gynecology Service, Hospital Materno Infantil, Goiânia, PO Box 6111, Universidade Estadual de Campinas – UNICAMP, Medical School -ZIP Code 13083-887, Campinas (SP), Brazil.

Author for Correspondence: Aarão M. Pinto-Neto, MD, PhD, Department of Gynecology and Obstetrics, Universidade Estadual de Campinas. Rua Alexander Fleming, 101, Cidade Universitária ‘‘Zeferino Vaz’’, 13083-970, Campinas, SP, Brazil.

Phone/Fax: +55 19 3521 9306; E-mail address: aarao@unicamp.br

Abstract

Purpose: To evaluate quality of life (QOL) in gynecologic cancer survivors after radiotherapy (RT), investigate the frequency of adverse events and demonstrate an association between these symptoms and QOL. **Methods:** A prospective cohort study of 95 women aged 21-75 years undergoing RT for gynecologic cancer was carried out. QOL was assessed by the WHOQOL-BREF before, at 4 months, 1 year and 3 years after RT and adverse events were evaluated following RT by the (CTCAE) v 3.0 scale. QOL scores were assessed by the Wilcoxon signed rank test over time. Multiple linear regression analysis was used to identify predictors of QOL. **Results**: The most frequent adverse events were pain (64.2%) and dyspareunia (45.9%). A significant increase in QOL scores was observed in the psychological domain, general health and overall QOL. Pain was negatively associated with the physical, psychological and social relationship domains ($p<0.01$); dyspareunia with the physical and social relationship ($p<0.01$); decreased sexual interest with the psychological ($p<0.01$). Higher family income was positively associated with the psychological domain and general health ($p<0.01$). **Conclusions:** Results suggested that QOL improved after RT in women with gynecologic cancer. Adverse events, such as pain, dyspareunia and decreased sexual interest had a negative impact on QOL.

Keywords: Gynecologic cancer, Quality of life, Adverse events, Radiotherapy

Introduction

Radiotherapy, surgery and chemotherapy are treatment modalities commonly used for the treatment of gynecologic cancer. However, these types of treatment are related to significant adverse effects on physical comfort, body image, sexual functioning and quality of life [1]. These different modes of treatment are combined to improve the survival rate in gynecologic cancer patients [2, 3], although these modalities have been related to the appearance of late side effects [4]. Late side effects are defined as those that occur 3 or more months after completion of radiotherapy treatment [5]. However, there is little data in the literature about the incidence of these late effects over time and especially the interference of these effects on QOL [6]. Measurement and assessment of cancer-related symptoms is a huge challenge because of the complex interaction between disease progression, multimodality treatments and symptoms [7].

Pelvic radiation therapy may be associated with changes in the gastrintestinal, urinary, gynecologic tracts and ovaries, resulting in adverse events such as diarrhea, vaginal and rectal bleeding, dysuria, urinary incontinence, hematuria, hot flashes, vaginal dryness, vaginal stenosis, dyspareunia and decreased sexual interest [8-11].

Acute side effects of RT generally subside within a short time and usually improve with medication. In contrast, late side effects are frequently irreversible, impairing QOL for prolonged periods of time and in some cases damage is permanent [2]. According to Bye et al [12], diarrhea was the most common symptom which negatively interfered with QOL up to 3-4 years after pelvic RT. Previous studies also reported a significant increase in complaints such as pain, dyspareunia and decreased sexual interest after pelvic radiotherapy [12-15]. Lack of intererest in sex and dyspareunia were highly negatively associated with QOL in women with cervical cancer after different treatment modalities, including radiation therapy [16].

Some authors have reported that sociodemographic characteristics exert little influence on QOL in gynecologic cancer patients when other variables are taken into consideration [17]. Similarly, in a previous study we confirmed that family income, age, school education and race were not associated with QOL in women with gynecologic cancer before starting radiation therapy [18]. Bradley et al

[19] also failed to observe an association between sociodemographic characteristics and quality of life after treatment. However, there have been few prospective studies on the factors that actually interfere with QOL.

Studies prospectively assessing QOL in gynecologic cancer patients documented an impaired QOL during and after completion of RT, which subsequently improved [20-23]. Although Barker et al [23] observed that certain adverse events had a negative impact on QOL in gynecologic cancer patients up to at least 2 years after RT, most studies did not evaluate the symptoms related to late cancer treatment effects, which usually appeared 2 to 3 years after treatment and interfered with QOL [24]. The aim of the present study was to prospectively evaluate QOL in women with gynecologic cancer up to 3 years after the completion of RT treatment, investigate the frequency of adverse events and demonstrate an association between these symptoms and QOL in a cohort of women with gynecologic cancer who had undergone pelvic radiotherapy treatment in a Brazilian public health institution.

Methods

A prospective cohort study was conducted in the Women's Hospital of the *Universidade Estadual de Campinas* Medical School, Campinas, Brazil, from March 2005 to March 2009. Participant selection was previously described in detail [25]. Briefly, women with cervical or endometrial cancer, ranging from 21 to 75 years of age were included in the study. Women with a previous history of pelvic radiation were ineligible. Of the 111 women selected, four refused to participate in the study, allegedly due to a lack of time. Therefore, 107 women were included in the study. Only 101 completed RT treatment and 95 returned for evaluation 30 days after treatment [25].

The present study therefore included 95 women. During the follow-up period, tumor recurrence, death and loss to follow-up excluded gynecologic cancer survivors from the study. Thus, 81 women returned for a follow-up visit at 4 months-T1 (8 were lost to follow-up, 6 were absent), 69 returned after one year-T2 (10 had tumor recurrence, 1 died, 5 were lost to follow-up, 2 were

absent), and 53 returned at 3 years- T3 (9 had tumor recurrence, 4 died, 4 were lost to follow-up, 01 was absent) after the completion of radiation therapy. Patients who missed the follow-up visit were not excluded from the study.

The majority of women (83.2%) received external pelvic radiotherapy and brachytherapy. The remaining women were given only external pelvic radiotherapy or brachytherapy, 37.4% underwent surgery and 17.8% received chemotherapy. Radiotherapy procedure has been previously described in detail [25]. Patients were not stratified by stage and cancer type, treatment modalities and age because despite the larger sample size compared to similar studies, the sample of this study was still too small to perform this type of analysis.

Assessment before radiotherapy included an interview and clinical evaluation. Participants were interviewed to investigate sociodemographic and clinical characteristics: age, race/ethnicity, level of education, marital status, monthly family income, employment status and menopausal status. Disease- and treatment-related data were gathered from medical records: cancer site, surgery, chemotherapy, cancer stage according to the International Federation of Gynecology and Obstetrics (FIGO). This study was approved by the Institutional Review Board and all women signed an informed consent form.

Evaluation adverse events

The frequency of adverse events was investigated according to the Common Terminology Criteria Adverse Event Scale (CTCAE) v 3.0 [26] that is a comprehensive grading system for the adverse events in cancer treatment. The occurrence of adverse events (diarrhea, dysuria, urinary incontinence, bleeding (vaginal, retal and vesical), dyspareunia, vaginal dryness, hot flashes and decreased sexual interest) was prospectively assessed by one of the researchers at 4 months (T1), 1 year (T2) and 3 years (T3) in follow-up visits after the completion of radiation therapy.

Quality of Life Assessment

For QOL assessment, a questionnaire of the World Health Organization's Quality of Life instrument-Abbreviated version was used (WHOQOL-BREF)

[WHOQOL GROUP, 1998] [27]. WHOQOL-BREF is a generic instrument used to assess QOL that has been translated and validated to the Portuguese language spoken in Brazil [28]. It is a multidimensional questionnaire, composed of 26 items, with 4 domains: physical health, psychological health, social relationships and environment. There are also 2 questions on overall QOL and general health. Higher scores indicate a better QOL. QOL was assessed prospectively by one of the researchers at the first medical consultation in the Radiotherapy Division before starting radiotherapy (T0), and at 4 months (T1), 1 year (T2), and 3 years (T3) during follow-up visits after the completion of radiotherapy. QOL was evaluated using the patients as their own controls over time.

Statistical analysis

The results were presented as medians, means and standard deviations (SD) or as absolute and relative frequencies, according to the type of variable. To calculate the prevalence and association of adverse events in QOL all women evaluated in each follow-up visit after RT were included. To evaluate QOL over time all women who had been evaluated in 4 points in time (T0 to T3) were taken into consideration.

QOL scores did not have a normal distribution and were evaluated over time using the ANOVA nonparametric test for repeated measures (Friedman). The Wilcoxon signed rank test (if significant) was also used to compare each time point in relation to baseline value. Bivariate analysis was used to identify predictors of QOL by the Mann-Whitney test. For multivariate analyses, QOL scores were considered dependent variables, and sociodemographic and clinical characteristics as well as adverse events were independent variables. Structural Equation Models (SEM) [29] with multiple linear regression analyses, calculation of the estimated parameter (EP) and coefficient of determination (R^2) with $P< 0.05$ were used. Multicollinearity in multivariate analysis was observed between bleeding and other variables for the QOL domains and one variable had to be excluded. The bleeding variable was chosen because it showed multicollinearity in various models. For data analysis, the SAS [30] program, Version 9.1 and AMOS program, version 5.0 were used.

Results

Sociodemographic and clinical characteristics of the participants before RT were previously described [25]. The median age of the participants was 60 years (range: 21-75 years). It was observed that the majority of patients (63.5%) had cervical cancer and at advanced stages of disease (III-IV), 75.7% reported a monthly family income of US$ 484.00 or lower, 77.6% had 4 or less years of school education and 54.2% were categorized as non-white. Following RT, the percentage of sexually active women during the 3-year study period was 45.7 %.(Data not shown in a table).

Table 1 shows the percentage and grade of adverse events in all time periods evaluated. After radiotherapy, 64.2% of the women experienced pain, 45.9% suffered from dyspareunia, 44.4% described having hot flashes, 44.4% had diarrhea, 30.9% suffered from bleeding (vaginal, anal, vesical) , 29.7% reported decreased sexual interest, 25.9 % experienced dysuria, 24.3% had vaginal dryness and 12.3% suffered from urinary incontinence during the period evaluated.

QOL scores are presented in Table 2. In comparison to scores measured before radiotherapy, QOL scores increased significantly in the following domains: physical in T1 (75.0±15.7; $p<0.01$) and psychological in T1 (71.5±14.0; $p<0.01$), T2 (71.6±12.4; $p=0.01$) and T3 (70.4±14.4; $p<0.01$); as well as overall QOL in T1 (76.1±16.1; $p<0.01$) and T3 (77.8±20.3; $p=0.01$). QOL scores increased in general health at all time periods: T1 (77.3±20.0; $p<0.01$), T2 (77.3±16.0; $p<0.01$), and T3 (74.4±19.8; $p=0.02$).

On bivariate analysis, it was observed that pain was negatively associated with the following domains: physical in T1 ($p<0.0030$), T2 ($p<0.0001$) and T3 ($p<0.0002$); psychological in T1 ($p<0.0123$), T2 ($p<0.0156$) and T3 ($p<0.0160$); environment in T1 ($p<0.0055$) and T3 (0.0204); social relationships in T1 ($p<0.0013$) and T3 ($p<0.0169$) as well general health in T2 ($p<0.0109$). Dysparunia negatively affected the following domains: physical in T3 ($p<0.0497$); psychological in T3 ($p<0.0369$); social relationships in T3 ($p<0.0231$) as well overall QOL in T2 ($p<0.0376$). Dysuria negatively interfered with the psychological domain in T3

(p<0.0367) and environment in T3 (p<0.0498). Bleeding interfered with overall QOL in T2 (p<0.0199) and decreased sexual interest interfered with overall QOL in T2 (p<0.0445) (Table 3).

On multivariate analysis, it was observed that 3 years after the completion of radiation therapy pain was negatively related to the following domains: physical (EP:-22.17; p=0.001), psychological (EP:-9.246; p=0.005), and social relationships (EP:-10.14; p=0.014). Dyspareunia was negatively associated with the domains of physical (EP:-13.417; p=0.003) and social relationships (EP:-11.67; p=0.019). Decreased sexual interest was negatively related to the psychological domain (EP:-19.37; p=0.001). A higher family income was positively associated with the psychological domain (EP: 0.008; p=0.001), and general health (EP: 0.010; p=0.016) (Table 4).

Discussion

The aim of the present study was to prospectively assess QOL in gynecologic cancer survivors after RT, investigate the frequency of adverse events and demonstrate an association between these symptoms and QOL. There was a significant improvement in QOL concerning the psychological domain, overall QOL and general health at 3 years after the completion of RT compared to baseline evaluation. Pain, dyspareunia and decreased sexual interest were the adverse events that most interfered with QOL 3 years after RT had ended.

Pain was the most frequent adverse event reported. Different types of pain (abdominal, leg, back, pelvic) were grouped together. As expected, the global rate of this symptom increased (64.2%) during the study period. However, the rates observed in different time periods (38.3% to 24.5%) were similar to those reported in other studies back and pelvic pain in 29% [13] and abdominal pain in 22.5% [31] of cervical cancer patients treated with RT.

It is well-known that diarrhea is a common complaint in gynecologic cancer patients after RT [12] and it may become a chronic problem [32]. We observed that 44.4% of women reported diarrhea. Similar rates of late gastrintestinal toxicity (50%) were observed in gynecologic cancer patients treated with conventional RT [33] and specifically diarrhea (43.2%) in those affected by cervical cancer [31].

Following RT, 44.4% of women reported suffering from hot flashes and 12.3% described being afflicted by urinary incontinence. Other researchers observed lower rates of hot flashes ranging from 6% [31] to 31.4% [34] in gynecologic cancer patients after receiving different treatment modalities. These differences may be explained by our cross-sectional study design and the inclusion of women treated for at least 2 years. Higher rates of urinary incontinence, 15% [35] to 25.2% [31] were observed in other studies, possibly because older patients treated for longer periods were included in those studies.

Previous studies have documented that vaginal bleeding was the most common symptom encountered in women with gynecologic cancer before RT which improved at the completion of therapy [13,18]. Nevertheless, according to Flay et al [13], vaginal bleeding was the most frequent symptom in women with gynecologic cancer after RT treatment. Those findings are in agreement with current data where 30.9% of women were afflicted by bleeding (vaginal, anal, vesical) during the study period. In cervical cancer patients treated with RT other authors found lower rates of dysuria: 8% [36] and14.4% [31], compared to the 25.9% observed in the present study. These differences may be explained by the cross-sectional study design.

During the study period, dyspareunia (45.9%) and decreased sexual interest (29.7%) were reported by sexually active women. Previous studies described 40-55% rates of dyspareunia in patients with gynecologic or uterine cervical cancer treated with different treatment modalities [37, 13, 11]. Lack of interest in sexual activities was observed by Wenzel et al [34] in 28.6% of women with cervical cancer postradiation treatment. A change in sexual desire since cancer diagnosis was reported in 65% of gynecologic cancer patients treated with RT or chemotherapy [37]. The difference in incidence of these effects may be attributed to the types of study and proportion of sexually active women. Prospective studies that assessed only sexually active women reported a higher incidence. Rates similar to those described in the present study (24.3% of vaginal dryness), were observed in previous studies: 21.6% [31] and 26% [38] in cervical cancer patients following different treatment modalities.

Despite the occurrence of different adverse events, there was an improvement in QOL after RT at all time periods studied (T1 to T3) in relation to baseline

evaluation (T0). However, some prospective studies have reported deterioration of QOL during and at completion of RT in patients with gynecologic [20, 21, 39, 23] and breast cancer [22] and improvement in QOL after radiation treatment, confirming current data. At 3 years since completion of RT, we observed that QOL scores improved significantly in the psychological domain and in both questions about overall QOL and general health. According to current data, in a previous evaluation emotional functioning was impaired in gynecologic cancer patients, improving after treatment [20, 21, 39,]. Global QOL improved in gynecologic cancer patients after treatment compared to baseline assessment [39] and global QOL improved in women with gynecologic cancer after RT [20].

General health had the worst QOL score in the baseline evaluation and scores increased significantly in the remaining time periods studied (T1 to T3). According to Vaz et al [18], some cancer symptoms were negatively associated with general health before starting radiation therapy in women with gynecologic cancer. It is noteworthy that the question on general health evaluated the subjective impression of health as perceived by women. It is likely that a recent cancer diagnosis, performance of surgery and cancer symptoms had negatively interfered with their perception of health before treatment. After RT and improvement in cancer symptoms, control of the disease and support offered by the institution may have contributed to a positive assessment of health status. As a result, there was a significant improvement in QOL scores for the question on general health in all time periods studied (T1 to T4).

Bivariate analysis showed that after radiotherapy, pain was significantly associated with a poorer QOL in the following domains: physical, psychological, environment, social relationships, and general health. It was also observed that women suffering from dyspareunia had lower scores in the domains of physical, psychological, social relationships and overall QOL. Dysuria was significantly associated with a poorer QOL for psychological and environment domains. Women who experienced bleeding and those who reported decreased sexual interest had lower scores in the overall QOL. Confirming current data, Vaz et al [18] observed that pain was associated with a worse QOL in the following domains:

physical, environment, overall QOL and general health in women with gynecologic cancer. Greimel et al [40] also observed a significant deterioration in QOL in cervical cancer patients treated with surgery and radiotherapy on various functioning scales (physical health, role emotional, cognitive and social functioning), in comparison to the remaining groups (control and surgery/chemotherapy) where urogenital and vaginal symptoms were significantly more frequent. In 2006, Bradley et al [19] reported a poorer overall QOL in women with gynecologic cancer who had persistent side effects after different treatment modalities. In agreement with those authors, our data showed a worse overall QOL in women who experienced pain, dyspareunia, dysuria, bleeding and decreased sexual interest.

Although previous studies had already reported an association between QOL and chronic radiation enteritis [41] and diarrhea [12] in gynecologic cancer patients after RT, this association was not observed in the present study. The reason may be that these women had a higher tolerance to this symptom. It is worth highlighting that Vaz et al [25] described that the most frequent symptom in women with gynecologic cancer during RT was gastrintestinal toxicity, although it did not interfere with QOL.

Pain, dyspareunia, decreased sexual interest and family income were predictors of QOL at the end of the study period. Pain was the most common symptom following radiotherapy. This may have contributed to the negative interference of this symptom in the physical, psychological, environment and social relationships domains after RT. According to Rummans et al [42], pain has a multifactorial origin and may affect all QOL dimensions, including the physical, social, psychological and spiritual components, confirming the current data. Other studies have reported a negative association between pain and QOL in gynecologic cancer patients before [18] and after RT [12].

Decreased sexual interest negatively interfered with the physical and psychological domains, and dyspaurenia interfered with the physical and social relationships domains at the end of the study period. Previous studies have found a significant increase in dyspaurenia in cervical cancer patients after pelvic radiotherapy [13, 15], and Frumovitz et al [14] described that cervical cancer survivors treated with radiotherapy had worse health-related QOL and sexual

functioning than did those treated with surgery. In 2007, Park et al [16] observed that lack of interest in sex and dyspareunia were highly associated with QOL (global health status; role emotional and social functioning) in cervical cancer patients after different treatment modalities. However these authors failed to report whether the association was negative or positive and data were not shown in a table. An association between dyspareunia and QOL (physical, psychological, environment, social relationship domains, overall QOL and general health) was also observed by Vaz et al [43] in gynecologic cancer patients after RT.

Family income was positively related to the physical, psychological domains and general health. The present study was conducted in a public health institution. Long before RT difficulties in accessing healthcare services had arisen, a delay in diagnosis and treatment and financial problems may have contributed to deterioration in QOL. In contrast, an increase in family income contributed to a positive perception of QOL after RT, since it may have minimized the barriers to information, transportation and treatment. In contrast, Bradley et al [19] did not observe any association between income and QOL in gynecologic cancer patients after treatment.

For data interpretation, some aspects must be considered. A decrease in sample size caused by patient exclusion (due to tumor recurrence, death and loss to follow-up) was a limiting factor, albeit expected. A reduction in sample size from 22.6% to 48.3% [32, 22, 23] was observed in studies where the ratio of stage III/IV disease was 30.4% to 41.5% and the study period was 2 to 3 years. Therefore, we believe that 50% information at the end of the study period allowed us to make an inference, since a decrease in sample size was expected and the proportion of women with stage III/IV disease was higher than that in other studies (63.5%). Sample size was small for the number of variables considered, even performing a statistical test that allowed us to use a smaller sample for this type of analysis. Further studies including a larger number of participants are needed to confirm the results observed. The use of a generic instrument (WHOQOL-BREF) for QOL assessment is also another limiting factor. However, when we began this study we had no knowledge of the existence of a

specific instrument that had been translated and validated to the Portuguese language. In contrast, cancer–specific QOL measures may not be the most suitable means to assess long-term survivors, because these measures are designed to capture the acute effects of receiving a recent cancer diagnosis and the immediate effects of surgery and treatment [44].

Nevertheless, the use of a generic instrument enabled us to identify factors that interfered with QOL over time. Despite its limitations, this study was probably the first to evaluate a higher proportion of women with advanced gynecologic cancer (stages III/IV) during a 3-year period and the adverse events that interfered with QOL in these women. This study contributed significantly to show that changes in QOL over time did not differ from studies that included a larger number of women with early-stage tumors (stages I/II) [20-23] i.e. QOL improves after treatment It also identified adverse events associated with QOL, demonstrating the limitations inherent in this type of study and its implications for data analysis.

In the present study, we used a standardized and internationally validated QOL questionnaire as well as a widely used (CTCAE) v 3.0 scale. A longitudinal study permitted a more accurate evaluation of the occurrence of adverse events in gynecologic cancer patients after RT which is usually underreported. Knowledge of the frequency and duration of these effects and their interference with QOL over time may allow us to provide better medical care and adequate psychological support to minimize their repercussions on QOL in these women. This may have been the first study in Brazil that prospectively evaluated the adverse events that interfere with QOL in gynecologic cancer patients.

Conclusion

In conclusion, we believe that these results are of interest to professionals involved in the management of gynecologic cancer patients. Knowledge of the frequency, duration and interference of adverse RT effects on QOL may enable us to implement interventions to minimize these symptoms and improve QOL. Although QOL in these women improved after treatment compared to a previous evaluation, pain, dyspareunia and decreased sexual interest negatively interfered

with QOL at the end of the study period. However, further studies are needed to confirm these results in other populations, including a larger number of women to identify the interference of these effects (as well as others) on QOL, and evaluate the repercussion of these interventions on QOL.

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Table 1. Frequency of adverse events during the study period, at 4 months (T1), at 1 year (T2) and at 3 years (T3) after RT and total (T1-T3)

Variables	T1(N=81) N (%)	T2(N=69) N (%)	T3(N=53) N (%)	Total (T1-T3) N (%)
Pain				
Grade I/II/III	31 (38.3)	24 (34.7)	13 (24.5)	52 (64.2)
Diarrhea				
Grade I/II	16 (19.7)	17 (24.6)	8 (15.0)	36 (44.4)
Hot flashes				
Grade I/II	30 (37.0)	19 (27.5)	11 (20.9)	36 (44.4)
Urinary incontinence				
Grade I/II	2 (2.5)	3 (4.3)	10 (18.9)	10 (12.3)
Bleeding				
Grade I/II	5 (6.2)	10 (14.5)	10 (18.9)	25 (30.9)
Dysuria				
Grade II	10 (12.3)	5 (7.2)	7 (13.2)	21 (25.9)
Dyspareunia*				
Grade I/II/III	11 (35.5)	9 (29.0)	8 (34.8)	17 (45.9)
Decreased sexual interest*				
Grade I/II	6 (19.4)	10 (32.3)	6 (26.1)	11 (29.7)
Vaginal dryness*				
Grade I/II	6 (19.4)	3 (9.7)	2 (8.6)	9 (24.3)

*Only sexually active women included.

Table 2. Quality of life scores in gynecologic cancer survivors before (T0) and at 4 months (T1), 1 year (T2), and 3 years (T3) after radiotherapy (N=44)

Domains	T0	T1xT0		T2xT0		T3xT0	
	Mean (SD)	Mean (SD)	p-value*	Mean (SD)	p-value*	Mean (SD)	p-value*
Physical	68.0 (17.0)	75.0 (15.7)	0.0087	71.5 (17.6)	0.2398	71.9 (16.8)	0.1063
Psychological	65.8 (14.9)	71.5 (14.0)	0.0073	71.6 (12.4)	0.0100	70.4 (14.4)	0.0070
Social relationship	79.1 (12.4)	81.9 (10.3)	0.1913	81.9 (12.7)	0.2121	81.2 (14.3)	0.4648
Environment	63.8 (11.8)	65.8 (10.6)	0.2583	67.9 (12.8)	0.0560	67.5 (12.6)	0.0942
Overall QOL	67.1 (17.7)	76.1 (16.1)	0.0049	73.3 (18.2)	0.0874	77.8 (20.3)	0.0120
General health	63.6 (20.5)	77.3 (20.0)	0.0002	77.3 (16.0)	0.0003	74.4 (19.8)	0.0204

Time effect by Friedman Anova for Repeated Measures $p < 0.05$ to all domains.*Wilcoxon signed rank test.

Table 3. Factors associated with quality of life in gynecologic cancer survivors according to time since radiotherapy. Bivariate analysis

Variables			T1(n=81) Mean (SD)	p-value	T2(n=69) Mean (SD)	p-value	T3(n=53) Mean (SD)	p-value
Physical	Pain	Yes	64.8 (16.0)	0.0030	55.4 (18.7)	0.0001	53.3 (18.6)	0.0002
		No	75.0 (14.3)		74.6 (16.1)		77.1 (12.2)	
	Dyspareunia*	Yes	73.7 (12.9)	0.7890	61.9 (20.1)	0.2122	62.5 (19.2)	0.0497
		No	72.5 (12.7)		71.3 (15.2)		77.1 (10.2)	
Psychological	Pain	Yes	64.7 (17.3)	0.0123	65.3 (13.7)	0.0156	60.6 (17.7)	0.0160
		No	74.5 (11.0)		74.1 (13.0)		74.1 (11.3)	
	Dyspareunia*	Yes	74.2 (9.1)	0.5326	65.3 (16.1)	0.2037	64.1 (11.8)	0.0369
		No	74.0 (10.2)		73.5 (12.6)		76.1 (6.0)	
	Dysuria	Yes	69.2 (18.6)	0.9025	66.7 (5.1)	0.1458	58.3 (18.9)	0.0367
		No	71.0 (13.9)		71.3 (14.2)		72.6 (12.6)	
Environment	Pain	Yes	60.6 (12.6)	0.0055	64.2 (11.6)	0.1609	60.5 (8.8)	0.0204
		No	68.4 (10.7)		68.0 (13.4)		69.6 (12.9)	
	Dysuria	Yes	65.9 (13.5)	0.9427	60.6 (3.6)	0.1684	57.1 (11.1)	0.0498
		No	65.4 (11.9)		67.2 (13.2)		68.9 (12.1)	
Social relationship	Pain	Yes	75.3 (12.4)	0.0013	78.3 (15.0)	0.3568	71.2 (14.3)	0.0169
		No	84.0 (11.4)		82.2 (13.8)		83.7 (13.6)	
	Dyspareunia*	Yes	83.3 (12.4)	0.3307	68.5 (16.0)	0.0512	65.6 (16.9)	0.0231
		No	79.8 (10.1)		81.4 (13.6)		80.6 (9.8)	
Overall QOL	Dyspareunia*	Yes	77.3 (17.5)	0.8043	63.9 (18.2)	0.0376	68.8 (25.9)	0.0969
		No	75.0 (16.2)		79.6 (14.7)		86.7 (12.9)	
	Bleeding	Yes	75.0 (17.7)	0.9640	55.6 (27.3)	0.0199	82.5 (16.9)	0.4849
		No	74.3 (16.3)		75.4 (15.7)		76.7 (20.7)	
	Decreased sexual interest*	Yes	75.0 (15.8)	0.8102	65.6 (12.9)	0.0445	68.8 (12.5)	0.1236
		No	76.0 (16.9)		78.3 (17.4)		82.9 (20.5)	
General health	Pain	Yes	72.6 (16.3)	0.1369	63.5 (24.4)	0.0109	69.2 (20.8)	0.1418
		No	78.0 (20.0)		78.4 (20.6)		78.1 (18.9)	

Mann-Whitney test. *Included only sexually active women

Table 4. Factors associated with quality of life in gynecologic cancer survivors three years after radiotherapy. Multivariate analysis. (N=53)

Domains	Variables	Estimated parameter	p-value	R2	p-value
Physical	Pain	-22.170	0.001	0.495	<0.001
	Dyspareunia	-13.417	0.003		
Psychological	Pain	-9.246	0.005	0.625	<0.001
	Decreased sexual interest	-19.370	0.001		
	Family income	0.008	0.001		
Social relationships	Dyspareunia	-11.670	0.019	0.257	<0.048
	Pain	-10.140	0.014		
General health	Family income	0.010	0.016	0.157	<0.001

R2: coefficient of determination. Variables considered in the analysis: age, cancer site, cancer stage, family income, race/ethnicity, school education, hot flashes, pain, diarrhea, dysuria, stress urinary incontinence, dyspareunia, decreased sexual interest and vaginal dryness.

4. Discussão

Os objetivos do presente estudo foram avaliar a QV de mulheres com câncer ginecológico, investigar a frequência de eventos adversos antes e após a radioterapia e verificar a associação desses efeitos com a QV dessas mulheres. No primeiro artigo avaliou-se a QV dessas mulheres antes da radioterapia, identificando os seus fatores associados. No segundo artigo investigou-se a proporção de mulheres sexualmente ativas, a frequência de sintomas sexuais e da menopausa, avaliou-se a QV dessas mulheres identificando os seus preditores. No terceiro artigo analisou-se a QV dessas mulheres, investigou-se a frequência de eventos adversos após a radioterapia e a associação desses sintomas com a QV.

Antes do início da radioterapia observou-se que o domínio meio ambiente e a questão relacionada à saúde geral eram os mais prejudicados e os sintomas do câncer foram os fatores de maior interferência na QV. Dor, sangramento, náusea, vômito e anemia associaram-se negativamente à QV dessas mulheres e cirurgia positivamente.

Em contraste com muitos instrumentos para avaliação de QV, o questionário WHOQOL-BREF inclui o domínio meio ambiente que, entre outros aspectos, avalia as dificuldades de acesso ao serviço de saúde e problemas financeiros. Portanto, o domínio meio ambiente desempenha um importante papel na determinação do estado de saúde, limitando ou facilitando o acesso aos serviços de saúde (59). Como o estudo foi realizado em uma instituição pública, dificuldades de acesso ao serviço de saúde, problemas financeiros, demora para o diagnóstico e tratamento podem ter contribuído para deterioração da QV no domínio meio ambiente antes do início do tratamento.

Maior comprometimento da QV foi observado para a saúde geral. Isso pode ser explicado pela associação negativa de alguns sintomas do câncer com a saúde geral antes da radioterapia. Cabe lembrar que essa questão avalia a impressão subjetiva das mulheres em relação à sua saúde, e é possível que o diagnóstico recente da doença, a realização de cirurgia e os sintomas do câncer estivessem interferindo negativamente na percepção de saúde dessas mulheres antes do tratamento.

Os sintomas relacionados ao câncer podem ser sistêmicos, como anemia, fadiga e perda de peso, ou localizados, como dor e sangramento (60). No presente estudo, dor foi o sintoma mais frequente, 49,5%. De acordo com estudo prévio, dor tem origem multifatorial, podendo afetar todas as dimensões da QV, incluindo os componentes físico, social, psicológico e espiritual (61), confirmando os dados atuais que mostram interferência negativa desse sintoma no domínio físico, QV global e saúde geral.

A progressão tumoral em mulheres com câncer ginecológico resulta em dor pélvica e sangramento vaginal (60). O sangramento vaginal pode influenciar negativamente a QV, agravando a anemia ou ocasionando constrangimento social. Além disso, pode ser interpretado como uma progressão da doença, prejudicando a percepção da melhora do quadro clínico, o que pode explicar em parte sua associação negativa com a saúde geral, como observado no presente estudo, onde 36,9% das mulheres referiram sangramento vaginal antes do início da radioterapia. Portanto, o sangramento vaginal pode influenciar a QV de forma direta, afetando a autopercepção da saúde geral, ou indiretamente, comprometendo o domínio físico, dificultando o manejo do quadro clínico relacionado à anemia.

Anemia foi referida por 22,3% das mulheres, sendo inferior à descrita em estudo prévio de 49,1% (62). Possivelmente, essa diferença deve-se ao fato de nesta casuística terem sido avaliadas apenas mulheres que não haviam se submetido à quimioterapia e/ou à radioterapia previamente. Embora seja um sintoma subjetivo e relativamente negligenciado, a ocorrência de náuseas associa-se à inapetência com possível perda de peso e prejuízos à QV (63). Náuseas e vômitos, à semelhança da anemia, podem contribuir para a ocorrência de fadiga, com diminuição da capacidade funcional. Esse quadro é consistente com a relação observada no presente estudo entre anemia, náusea/vômito e pior QV para o domínio físico.

Por outro lado, a associação observada entre cirurgia e QV é contraintuitiva. Apesar da morbidade da cirurgia, é possível que ela seja vista como uma possibilidade de cura, explicando sua interferência positiva na QV

para a saúde geral neste estudo. Porém, esse achado necessita ser investigado em estudos delineados especificamente para esse objetivo.

Alguns estudos mostraram associações de outros fatores com a QV (52,53), que tendem a desaparecer com o tempo. Na análise bivariada, diversos fatores associaram-se negativamente à QV. Mas, quando se consideraram conjuntamente todas as variáveis, apenas os sintomas do câncer afetaram negativamente a QV. Confirmando os achados deste estudo, Wan et al.(58) referiram que os fatores sociodemográficos exercem pouca influência na QV de pacientes com câncer quando outras variáveis são controladas.

Após a radioterapia, verificou-se um aumento significativo do número de mulheres sexualmente ativas em relação à avaliação prévia e melhora da QV para o domínio psicológico, e para as questões QV global e saúde geral três anos após o tratamento em relação à avaliação inicial. Analisando apenas os sintomas sexuais e da menopausa, dispareunia foi o único sintoma com interferência negativa na QV no final do período avaliado. Entretanto, quando se analisaram todos os efeitos estudados – dor, dispareunia e diminuição do interesse sexual – verificou-se que estes estavam interferindo negativamente na QV no final do período avaliado (3 anos). A renda familiar associou-se positivamente à QV nas duas análises.

O aumento significativo de mulheres sexualmente ativas em relação à avaliação inicial, de 21,5% para 44,2% após três anos, indica prejuízo da função sexual antes da radioterapia relacionado ao diagnóstico do câncer, cirurgia e sintomas como dor e sangramento vaginal. A função sexual de mulheres com

câncer ginecológico pode estar comprometida por sintomas como corrimento vaginal, dor e sangramento (64). Consistente com os dados atuais, foi reportado que antes da radioterapia 15% das mulheres com câncer do endométrio eram sexualmente ativas e após um ano do tratamento essa proporção foi de 39% (65). Outros autores relataram diminuição da percentagem de mulheres sexualmente ativas após a radioterapia (22), sendo que apenas 63% delas continuavam sexualmente ativas um ano após o tratamento e isto pode ter relação com a avaliação inicial retrospectiva, mesmo sendo a maioria portadora de tumores em estágio inicial (I/II).

Dor foi o evento adverso mais frequente. O agrupamento de diferentes tipos de dor (abdominal, pélvica, lombar e nas pernas) elevou a frequência total desse sintoma (64,2%) durante o período avaliado. Contudo, as taxas observadas nos diferentes momentos avaliados (38,3% a 24,5%) são similares às de outros estudos – 29% (dores pélvica e lombar) em pacientes com câncer cervical tratadas com radioterapia (27) e 22,5% (dor abdominal) (25).

Diarreia é um sintoma comum em pacientes com câncer ginecológico após a radioterapia (23) que tende a se tornar um problema crônico (24), confirmando os dados atuais em que 44,4% das mulheres referiram diarreia. Taxas similares de toxicidade gastrintestinal tardia (50%) foram observadas em pacientes com câncer ginecológico tratadas com radioterapia convencional (40) e de diarreia (43,2%) naquelas com câncer cervical após a radioterapia (25).

Após a radioterapia, 44,4% das mulheres referiram ondas de calor e 12,3% incontinência urinária. Aumento significativo de ondas de calor foi observado apenas na primeira avaliação após a radioterapia em relação à avaliação prévia (24% vs 37%), com diminuição nas avaliações seguintes. A diminuição de ondas de calor após um ano de tratamento não é explicada pela TH, pois apenas 1,2% das mulheres estava em uso de TH, e pode ter relação com menor duração desse efeito em pacientes com câncer ginecológico, sendo necessários novos estudos para comprovar esses dados. Outros pesquisadores observaram taxas inferiores de ondas de calor de 6% (25) a 31,4% (66) (em pacientes com câncer ginecológico após diferentes modalidades de tratamento). Essas diferenças podem ser explicadas pelo desenho do estudo de corte transversal e por incluírem mulheres tratadas há pelo menos dois anos. Taxas superiores de incontinência urinária, de 15% (67) a 25,2% (25), foram observadas em outros estudos. No presente estudo, 12,3% apresentaram incontinência urinária. A inclusão de pacientes mais velhas e o maior tempo após tratamento nos estudos anteriores podem explicar a diferença.

Sangramento vaginal é um sintoma frequente em mulheres com câncer ginecológico antes da radioterapia, com melhora no final do tratamento (27, 57). Entretanto, de acordo com outro estudo (27), sangramento vaginal foi um sintoma frequente em mulheres com câncer ginecológico após a radioterapia e está de acordo com os dados atuais, em que 30,9% das mulheres apresentaram sangramento (vaginal, anal, vesical) durante o período avaliado. Taxa inferior de disúria, de 8% (20) a 14,4% (25), foi observada em pacientes com câncer de

colo uterino após a radioterapia, e no presente estudo 25,9% apresentaram esse sintoma. Essas diferenças podem ser explicadas pelo desenho do estudo corte transversal nos estudos prévios.

Durante o período avaliado, 45% das mulheres sexualmente ativas referiram dispareunia e 29,7% diminuição do interesse sexual. Estudos prévios relatam taxas de 40% a 55% de dispareunia em pacientes com câncer ginecológico ou cervical após diferentes modalidades de tratamento (22,27,36). Observou-se aumento significativo de dispareunia até um ano após a radioterapia, de acordo com os resultados deste estudo, e outros autores também relataram aumento desse sintoma após a radioterapia (27,32). Diminuição do interesse sexual também foi observado em 28,6% (66) das mulheres com câncer de colo do útero após diversas modalidades de tratamento, e alteração no desejo sexual após o diagnóstico do câncer em 65% das pacientes com câncer ginecológico tratadas com radioterapia ou quimioterapia (36). A diferença na incidência desses efeitos está relacionada ao tipo de estudo e proporção de mulheres sexualmente ativas.

Taxas similares às do presente estudo - 24,3% para secura vaginal - foram observadas em estudos prévios, de 21,6% (25) e 26% (33), em pacientes com câncer de colo do útero após diferentes modalidades de tratamento. Contudo, observou-se diminuição significativa da secura vaginal, três anos após a radioterapia, em relação à avaliação prévia (8,3% vs 26,7%) e pode ter relação com o uso de lubrificantes vaginais por 40,5% das mulheres após a primeira avaliação.

Mesmo com a ocorrência de vários eventos adversos houve melhora da QV após a radioterapia em todos os momentos analisados (T1 a T3) em relação à avaliação prévia (T0). Estudos prospectivos têm relatado piora da QV durante e no final da radioterapia em pacientes com câncer ginecológico (7,51,52,55) e de mama (53) e melhora da QV após o tratamento,confirmando os dados atuais. Ao final de três anos após o tratamento verificou-se melhora significativa dos escores de QV para o domínio psicológico e para as duas questões QV global e saúde geral.

De acordo com o presente estudo, o comprometimento da função emocional foi observado em pacientes com câncer ginecológico na avaliação prévia, com melhora após o tratamento (7,51,52) e melhora da QV Total em pacientes com câncer ginecológico um ano após o tratamento em relação à avaliação inicial (7) e da QV Global após a radioterapia (51).

A questão saúde geral era a mais comprometida na avaliação inicial, com aumento significativo dos escores de QV para os demais momentos avaliados (T1 a T3). De acordo com estudo prévio (57), alguns sintomas do câncer estavam negativamente associados à Saúde geral antes da radioterapia em mulheres com câncer ginecológico. Como essa questão avalia a impressão subjetiva das mulheres em relação à sua saúde, é possível que diagnóstico recente, cirurgia e sintomas do câncer estivessem interferindo negativamente na percepção de saúde desse grupo antes do tratamento. Após a radioterapia, melhora dos sintomas do câncer, controle da doença e o suporte oferecido pela instituição podem ter contribuído para a avaliação positiva do S*tatus* de saúde e,

consequentemente, para uma melhora significativa dos escores de QV para a Saúde geral em todos os momentos avaliados.

A análise bivariada mostrou que após a radioterapia, dor estava significativamente associada à piora da QV para os domínios: físico, psicológico, relacionamento social, meio-ambiente e para a saúde geral. Mulheres com dispareunia apresentavam menor escore de QV para os domínios físico, psicológico e relacionamento social e para a QV global. Disúria estava significativamente associada à piora na QV para os domínios: psicológico e meio-ambiente. Mulheres com sangramento e aquelas com diminuição do interesse sexual tinham menor escore para a QV global. Confirmando os dados atuais, Rummans et. al. (61) relatam que a origem da dor é multifatorial e pode afetar todas as dimensões da QV, incluindo os domínios físico, social, psicológico e espiritual. Comprometimento significativo da QV em várias escalas funcionais (físico, papel, cognitivo e social) também foi observado em pacientes com câncer cervical tratadas com cirurgia e radioterapia em relação aos demais grupos (controle e cirurgia/quimioterapia) onde os sintomas urogenitais e vaginais foram significativamente maiores (62). Em 2006, Bradley et al. (46) relatam piora da QV global em mulheres com câncer ginecológico que continuaram apresentando efeitos colaterais após diversas modalidades de tratamento. Correlação inversa entre sintomas e QV foi observada em outros estudos (8,52,57). Em concordância com esses autores, os dados deste estudo mostram pior QV para mulheres com dor, dispareunia, diminuição do interesse sexual e sangramento.

Embora associação negativa entre QV e diarreia tenha sido relatada em pacientes com câncer ginecológico após a radioterapia (23), essa associação não foi observada no presente estudo. Isso pode ter relação a uma maior tolerância a esse sintoma por essas mulheres, pois segundo estudo prévio toxicidade gastrintestinal foi o sintoma mais frequente em mulheres com câncer ginecológico durante a radioterapia sem interferência na QV (69).

Dor, dispareunia, diminuição do interesse sexual e renda familiar foram os preditores da QV três anos após a radioterapia. Dor foi o efeito adverso mais frequente e isso pode ter contribuído para sua interferência negativa nos domínios físico, psicológico e relacionamento social. Segundo Rummans et al. (61), a dor tem origem multifatorial e pode afetar todas as dimensões da QV, confirmando os dados atuais. Associação negativa entre dor e QV foi relatada em pacientes com câncer ginecológico antes (57) e após (23) a radioterapia.

Diminuição do interesse sexual interferiu negativamente nos domínios físico e psicológico e dispareunia nos domínios físico e relacionamento social. Estudos prévios relatam aumento significativo de queixas de dispareunia em pacientes com câncer cervical após a radioterapia (27,32) e pior QV e função sexual para aquelas tratadas com radioterapia em relação às tratadas com cirurgia (10). Em 2007, Park et al (56) observaram que diminuição do interesse sexual e dispareunia estavam altamente associados com a QV (estado geral de saúde, papel, função emocional e social) em pacientes com câncer cervical após diferentes modalidades de tratamento. Entretanto, esses autores falharam em não relatar se a associação foi negativa ou positiva (dados não mostrados em tabela).

Renda familiar interferiu positivamente nos domínios físico, psicológico e na saúde geral. Como o estudo foi realizado em uma instituição pública, dificuldades de acesso ao serviço de saúde, problemas financeiros, demora para o diagnóstico e tratamento podem ter contribuído para deterioração na QV antes da radioterapia. Entretanto, após o tratamento, a maior renda pode ter contribuído para uma percepção positiva da QV, minimizado as dificuldades em relação a informações, transporte e seguimento após o tratamento. Contudo, a associação entre renda e QV não foi observada em mulheres com câncer ginecológico após o tratamento (46).

Para interpretação dos dados deste estudo, alguns aspectos devem ser considerados. A diminuição da amostra devido à exclusão por recidiva, óbito e perda de seguimento foi um fator limitante, mas esperado. Redução de 22,6% a 48,3% da amostra foi observada em estudos onde a proporção de estágio III/IV foi de 30,4% a 41,5% e o período avaliado foi de 2 a 3 anos (24,53,55). Dessa forma, acreditamos que 50% das informações no final do período avaliado contribuem para inferência, uma vez que a diminuição da mostra era esperada, a proporção de mulheres em estágio III/IV foi maior em relação à de outros estudos (63,5%) e o período avaliado foi de 3 anos. Entretanto, os resultados devem ser interpretados com cuidado. Como a amostra é pequena para o número de variáveis consideradas, mesmo o teste utilizado permitindo uma amostra menor para esse tipo de análise, são necessários novos estudos com um número maior de pacientes para confirmar esses resultados. A amostra não foi estratificada por estágio e tipo de câncer, idade e modalidade de tratamento.

Isso também é considerado um fator limitante neste estudo. Apesar de tudo, acreditamos que em termos clínicos houve pouca influência nos resultados, pois, de acordo com estudos prévios, estágio (46,53) e localização do câncer (52) não estiveram associados à QV de mulheres com câncer ginecológico após o tratamento. Dessa forma, uma maior proporção de mulheres com câncer de colo do útero (63.5%) não alterariam os resultados em relação à QV, e eventos adversos. Estudos prévios relatam pior QV (47,68) e maior frequência de sintomas da menopausa e sexual (10) para mulheres tratadas com radioterapia em relação às tratadas com cirurgia ou quimioterapia. Como todas as mulheres foram tratadas com radioterapia, outras modalidades de tratamento teriam pouca influência nos resultados do presente estudo. Outra limitação foi não termos avaliado o impacto da idade na função sexual devido ao tamanho da amostra, que foi muito pequena para esse tipo de análise. Entretanto, sabe-se que maior idade está associada à diminuição da atividade sexual (70).

A utilização de um instrumento genérico (WHOQOL-ABREVIADO) (71,72) para avaliação da QV também é outro fator limitante. Entretanto, quando iniciamos o estudo não tínhamos conhecimento de nenhum instrumento especifico traduzido e com validade para a língua portuguesa. Por outro lado, instrumento de QV específico para o câncer pode não ser o mais apropriado para avaliar pacientes após anos de tratamento, pois geralmente são desenhados para avaliar efeitos agudos, em pacientes com câncer, com diagnóstico recente e efeitos imediatos após cirurgia e tratamento (73). Outra limitação desse questionário é não dispor de domínio específico para avaliar a função sexual. Entretanto, este domínio

pode não ser adequadamente avaliado através de instrumento específico para pacientes com câncer (74). Porém, até o momento não há um instrumento que possa ser recomendado para avaliação da função sexual em pacientes com câncer ginecológico (75).

Contudo, a utilização de um instrumento genérico permitiu a identificação de fatores que estavam interferindo na QV antes do início da radioterapia e ao longo do tempo. Apesar das limitações, provavelmente esse foi o primeiro estudo a avaliar uma maior proporção de mulheres com câncer ginecológico em estágio mais avançado (III/IV) por um período de 03 anos e a interferência de eventos adversos na QV dessas mulheres. As suas principais contribuições foram mostrar que as alterações da QV ao longo do tempo não diferem dos estudos com maior proporção de mulheres em estágios iniciais (I/II) (51-53,56), ou seja, a QV melhora após o tratamento. Outra contribuição foi identificar os eventos adversos associados à QV antes e após a radioterapia; mostrar as limitações inerentes a este tipo de estudo e suas implicações na análise dos dados.

No presente estudo utilizamos um questionário de QV padronizado e validado internacionalmente, assim como a escala (CTCAE) v 3.0 (45). O estudo longitudinal possibilitou uma avaliação mais precisa da ocorrência de eventos adversos em mulheres com câncer ginecológico após a radioterapia usualmente não reportada. O conhecimento da frequência e duração desses efeitos e sua interferência na QV ao longo do tempo permitirão oferecer melhores cuidados clínicos e suporte psicológico adequado para minimizar sua repercussão na QV dessas mulheres. Serão necessários novos estudos que avaliem as intervenções

e tratamentos disponíveis para a dispareunia, diminuição dos interesses sexual e dor e para outros eventos adversos. Pois embora a dor seja um sintoma bem estudado e caracterizado (76), neste estudo interferiu negativamente em várias dimensões da QV dessas mulheres antes e após a radioterapia. Quanto à dispareunia há pouca evidência de que o uso de dilatador vaginal previne efeitos tardios da radioterapia, melhorando a função sexual e a QV de mulheres com câncer ginecológico (77).

Acreditamos que os resultados deste estudo sejam de interesse para profissionais envolvidos no cuidado de pacientes com câncer ginecológico, pois o conhecimento em relação à frequência, duração e interferência dos sintomas do câncer antes do tratamento e dos eventos adversos após a radioterapia na QV possibilitam a implementação de intervenções que minimizem esses sintomas, visando a melhorar a QV. Embora o número de mulheres sexualmente ativas tenha aumentado e a QV tenha melhorado após o tratamento em relação à avaliação prévia, a dor, dispareunia e diminuição do interesse sexual interferiram negativamente na QV no final do período avaliado. Entretanto, para confirmar estes resultados são necessários novos estudos, em outras populações, que incluam maior número de mulheres, que identifiquem a interferência destes e de outros efeitos na QV, e que avaliem a repercussão de intervenções utilizadas para melhorar a QV.

5. Conclusões

- O domínio meio ambiente e a questão relacionada à saúde geral eram os mais comprometidos antes do início da radioterapia. Os sintomas do câncer foram os fatores de maior interferência na QV.

- Houve aumento significativo do número de mulheres sexualmente ativas três anos após a radioterapia e diminuição das queixas de secura vaginal. Observou-se ainda melhora da QOL, sendo que a dispareunia afetou negativamente várias dimensões da QOL.

- Os resultados sugerem que a QV melhora após a radioterapia em mulheres com câncer ginecológico. Eventos adversos como dor, dispareunia e diminuição do interesse sexual interferiram negativamente na QV no final do período avaliado.

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7. Anexos

7.1. Anexo 1 – Termo de Consentimento Livre e Esclarecido

Toxicidade aguda da radioterapia e qualidade de vida em mulheres com neoplasia genital

Eu, _____
RG nº _____, fui informada de que está sendo realizada uma pesquisa no CAISM – UNICAMP com mulheres portadoras de neoplasia do colo do útero ou do útero e que farão tratamento de radioterapia. O objetivo desta pesquisa é estudar os efeitos colaterais que podem ocorrer durante esse tratamento e avaliar a qualidade de vida dessas mulheres. Através desse conhecimento poderá ser dado um melhor atendimento médico a mulheres que farão tratamento radioterápico, e orientações adequadas em relação à possibilidade de ocorrência desses efeitos. Se eu concordar em participar da pesquisa irei responder um questionário agora e no final do tratamento, tendo a liberdade de deixar de responder as perguntas que não desejar. E que não serei submetida a nenhum exame ou procedimento adicional em virtude desta pesquisa.

Durante o tratamento terei consulta médica e de enfermagem semanal, para avaliação do tratamento e de possíveis efeitos colaterais, e a cada dez aplicações de radioterapia será colhido um exame de hemograma. Esses procedimentos fazem parte do tratamento, e eu, estando ou não participando da pesquisa eles serão realizados. E que as informações fornecidas por mim, observadas durante as consultas e as registradas no prontuário, serão utilizadas na pesquisa.

Um mês após o termino do tratamento terei um retorno conforme rotina do serviço, o que não me causará gastos diferentes daqueles de todas as outras mulheres atendidas aqui. Terei acesso às informações que solicitar no início e durante o andamento da pesquisa, podendo entrar em contato com a pesquisadora principal Ana Francisca Vaz pelo telefone 37889362 ou pessoalmente, diariamente na Seção de Radioterapia do CAISM. Poderei recusar-me a participar ou retirar-me da pesquisa a qualquer momento, sem nenhum prejuízo no meu tratamento. Também fui informada que o meu nome ou qualquer outro dado pelo qual eu possa ser identificada não serão divulgados, sendo do conhecimento apenas dos pesquisadores.

Se achar necessário eu poderei pedir esclarecimentos ou informações a respeito das questões éticas ao Comitê de Ética em Pesquisa da Faculdade de Ciências Médicas da UNICAMP pelo telefone 37888936.

Declaro que estou ciente de todas as informações prestadas e que concordo em participar deste estudo.

Campinas, ____ de _____ de 2005.

_____
Assinatura da participante

_____
Assinatura da pesquisadora principal

7.2. Anexo 2 – Ficha de Coleta de Dados

Toxicidade aguda da radioterapia e qualidade de vida em mulheres com neoplasia genital

Grupo: |___| 1.Câncer do colo do útero 2.Câncer do endométrio

Nº no estudo |___|___|

Data 1ª consulta: _____/_____/_____

Identificação da participante (a ser destacada)

Nome:_____

HC: |___|___|___|___|___|___-___| RT:_____/_____

Data 1ª consulta:___/_____/_____

Rua:_____ Nº_____

Complemento:_____

Bairro:_____

Cidade:_____ Est.:_____

Tel.: (_____)_____

Seção I - Características pessoais

1. 1 – Entrevistadora diga: "Gostaria de fazer algumas perguntas sobre a senhora":

1.1a Qual a sua idade?_____ anos
1.1b Qual a sua data de nascimento? ___/___/_____

1.2 Entre estas que eu vou ler, qual a senhora considera que é a sua cor ou raça: branca, preta, parda, amarela ou indígena?

(1) Branca
(2) Preta
(3) Parda
(4) Amarela
(5) Indígena
(6) Outra. Qual? _____

1.3 Qual foi a ultima série completa que a senhora frequentou na escola?

_____

1.4 Qual é a sua profissão?_____

1.5 Atualmente a senhora é solteira, casada, vive junto, separada ou viúva?

(1) Solteira
(2) Casada
(3) Vive junto
(4) Separada/ divorciada/ desquitada
(5) Viúva

1.6 A senhora apresenta algum desses sintomas?

(1) Dor
(2) Sangramento vaginal
(3) Disúria
(4) Náusea
(5) Vômito
(6) Diarreia
(7) Ondas de calor
(8) Nehum

1.2 – "Agora vou fazer algumas perguntas sobre menstruação e atividade sexual"

1.7 A senhora ainda menstrua?

(1) Sim (2) Não (3) Não sabe referir devido a sangramento

1.8 Há quanto tempo foi a sua última menstruação?_____

|_____|_____| Meses |_____|_____| Anos

1.9 A senhora já fez ou está fazendo TRH (terapia de reposição hormonal) ?

(1) Sim _____ (2) Não

1.10 A senhora já teve ou tem relações sexuais ?

(1) Sim (2) Nunca teve → terminar a entrevista

1.11 Nos últimos três meses a senhora teve relações sexuais com o parceiro (pela vagina)?
(1) Sim (2) Não → passe para 1.14

1.12 Quantas vezes por semana a senhora tem relações sexuais?
(1) Uma (2) Duas (3) Três (4) mais de três

1.13 A senhora tem apresentado algum desses sintomas quando tem relações sexuais?
(1) Sangramento
(2) Dispareunia
(3) Secura vaginal
(4) Falta de prazer
(5) Outro:_____
→ terminar a entrevista

1.14 Nos últimos três meses a senhora não teve atividade sexual por algum desses motivos?
(1) Não tem parceiro
(2) Devido à cirurgia
(3) Devido a sangramento vaginal
(4) Outro:_____

1.15 A senhora apresentava algum desses sintomas quando tinha relações sexuais?
(1) Sangramento
(2) Dispareunia
(3) Secura vaginal
(4) Falta de prazer
(5) Outro:_____

Gostaria de agradecer-lhe pela atenção e pelo tempo dedicado a responder às perguntas.

Seção II – Estadiamento, modalidades de tratamento e toxicidade

Os dados desta seção serão coletados do prontuário da paciente após o tratamento.

2.0 Estadiamento:_____

2.1 Realizou cirurgia ?
(1) Sim (2) Não

2.2 Tipo de cirurgia:_____

2.3 Realizou quimioterapia ?
(1) Sim (2) Não

2.4 Tratamento radioterápico realizado:
(1) Teleterapia (2) Braquiterapia (3) Teleterapia e braquiterapia

2.5 Dose total do tratamento de radioterapia:
Teleterapia: _____ Braquiterapia: _____

2.6 Duração do tratamento:
Início: ___/___/_____ Término: ___/___/_____

2.7 Toxicidade gastrintestinal alta:

Graduação	1ª revisão __/__/__	2ª revisão __/__/__	3ª revisão __/__/__	4ª revisão __/__/__	5ª revisão __/__/__	6ª revisão __/__/__	1º retorno __/__/__
Grau 0							
Grau 1							
Grau 2							
Grau 3							
Grau 4							

2.8 Toxicidade gastrintestinal baixa

Graduação	1ª revisão __/__/__	2ª revisão __/__/__	3ª revisão __/__/__	4ª revisão __/__/__	5ª revisão __/__/__	6ª revisão __/__/__	1º retorno __/__/__
Grau 0							
Grau 1							
Grau 2							
Grau 3							
Grau 4							

2.9 Toxicidade geniturinária

Graduação	1ª revisão __/__/__	2ª revisão __/__/__	3ª revisão __/__/__	4ª revisão __/__/__	5ª revisão __/__/__	6ª revisão __/__/__	1º retorno __/__/__
Grau 0							
Grau 1							
Grau 2							
Grau 3							
Grau 4							

2.10 Toxicidade dermatológica

Graduação	1ª revisão __/__/__	2ª revisão __/__/__	3ª revisão __/__/__	4ª revisão __/__/__	5ª revisão __/__/__	6ª revisão __/__/__	1º retorno __/__/__
Grau 0							
Grau 1							
Grau 2							
Grau 3							
Grau 4							

2.11 Toxicidade ginecológica:

Ondas de calor:

Graduação	1ª revisão __/__/__	2ª revisão __/__/__	3ª revisão __/__/__	4ª revisão __/__/__	5ª revisão __/__/__	6ª revisão __/__/__	1º retorno __/__/__
Grau 0							
Grau 1							
Grau 2							

Dispareunia

Graduação	1ª revisão __/__/__	2ª revisão __/__/__	3ª revisão __/__/__	4ª revisão __/__/__	5ª revisão __/__/__	6ª revisão __/__/__	1º retorno __/__/__
Grau 0							
Grau 1							
Grau 2							
Grau 3							

Libido

Graduação	1ª revisão __/__/__	2ª revisão __/__/__	3ª revisão __/__/__	4ª revisão __/__/__	5ª revisão __/__/__	6ª revisão __/__/__	1º retorno __/__/__
Grau 0							
Grau 1							
Grau 2							

Secura vaginal

Graduação	1ª revisão __/__/__	2ª revisão __/__/__	3ª revisão __/__/__	4ª revisão __/__/__	5ª revisão __/__/__	6ª revisão __/__/__	1º retorno __/__/__
Grau 0							
Grau 1							
Grau 2							

2.12 Toxicidade hematológica: WBC

Graduação	1º exame __/___/_____	2º exame __/___/_____	3º exame __/___/_____	4º exame __/___/_____
Grau 0				
Grau 1				
Grau 2				
Grau 3				
Grau 4				

Hemoglobina

Graduação	1º exame __/___/_____	2º exame __/___/_____	3º exame __/___/_____	4º exame __/___/_____
Grau 0				
Grau 1				
Grau 2				
Grau 3				

Hematócrito

Graduação	1º exame __/___/_____	2º exame __/___/_____	3º exame __/___/_____	4º exame __/___/_____
Grau 0				
Grau 1				
Grau 2				
Grau 3				

Plaquetas

Graduação	1º exame __/___/_____	2º exame __/___/_____	3º exame __/___/_____	4º exame __/___/_____
Grau 0				
Grau 1				
Grau 2				
Grau 3				
Grau 4				

Neutrófilos

Graduação	1º exame __/___/_____	2º exame __/___/_____	3º exame __/___/_____	4º exame __/___/_____
Grau 0				
Grau 1				
Grau 2				
Grau 3				
Grau 4				

2.13 Que tipo de tratamento foi utilizado:

(1) Transfusão de sangue
(2) Mediações
(3) Internação
(4) Cirurgia
(5) Nenhum
(6) Outro:_____

2.14 O tratamento foi interrompido devido à toxicidade aguda:

(1) Sim (2) Não

2.15 Qual foi a toxicidade? (assinalar todas as que levaram à interrupção do tratamento).

(1) Gastrintestinal Tempo_____
(2) Geniturinária Tempo_____
(3) Hematológica Tempo_____
(4) Dermatológica Tempo_____
(5) Ginecológica Tempo_____

2.16 No primeiro retorno a paciente apresentava alguns desses sintomas?

(1) Dor (3) Ondas de calor

(2) Sangramento v (4) Outro:_____

2.17.No primeiro retorno a paciente está tendo atividade sexual?

(1) Sim (2) Não

2.18.No primeiro retorno a paciente está fazendo TRH? :_____

2.19.Eventos adversos após a radioterapia:

Diarreia

Graduação	1º retorno __/___/_____	2º retorno __/___/_____	3º retorno __/___/_____
Grau 1			
Grau 2			
Grau 3			
Grau 4			
Grau 5			

Disúria

Graduação	1º retorno __/___/_____	2º retorno __/___/_____	3º retorno __/___/_____
Grau 1			
Grau 2			
Grau 3			
Grau 4			

Dor

Graduação	1º retorno __/___/_____	2º retorno __/___/_____	3º retorno __/___/_____
Grau 1			
Grau 2			
Grau 3			
Grau 4			

Sangramento

Graduação	1º retorno __/___/_____	2º retorno __/___/_____	3º retorno __/___/_____
Grau 1			
Grau 2			
Grau 2			
Grau 3			
Grau 4			
Grau 5			

Incontinência urinária

Graduação	1º retorno __/___/_____	2º retorno __/___/_____	3º retorno __/___/_____
Grau 1			
Grau 2			
Grau 3			
Grau 4			

Dispareunia

Graduação	1º retorno __/___/_____	2º retorno __/___/_____	3º retorno __/___/_____
Grau 1			
Grau 2			
Grau 3			
Grau 4			

Secura vaginal

Graduação	1º retorno __/___/_____	2º retorno __/___/_____	3º retorno __/___/_____
Grau 1			
Grau 2			

Diminuição do interesse sexual (libido)

Graduação	1º retorno __/___/_____	2º retorno __/___/_____	3º retorno __/___/_____
Grau 1			
Grau 2			

Ondas de calor

Graduação	1º retorno __/___/_____	2º retorno __/___/_____	3º retorno __/___/_____
Grau 1			
Grau 2			
Grau 3			

7.3. Anexo 3 – Questionário WHOQOL-BREF

Versão em Português do Instrumento de Avaliação de Qualidade de Vida da Organização Mundial da Saúde (WHOQOL – ABREVIADO) 1998.

Este questionário é sobre como a senhora se sente em relação à sua qualidade de vida, saúde e outras áreas de sua vida nas duas ultimas semanas. Eu vou ler cada pergunta com suas respostas; a senhora deverá escolher a resposta que lhe parecer mais adequada para o seu caso.

Q1 - Como você avaliaria sua qualidade de vida?

muito ruim	ruim	nem ruim nem boa	boa	muito boa
1	2	3	4	5

Q2 - Quão satisfeito(a) você está com a sua saúde?

muito insatisfeito	insatisfeito	nem satisfeito nem insatisfeito	satisfeito	muito satisfeito

As questões seguintes são sobre **o quanto** você tem sentido algumas coisas nas duas ultimas semanas.

Q3 - Em que medida você acha que sua dor (física) impede de fazer o que você precisa?

nada	muito pouco	mais ou menos	bastante	extremamente
1	2	3	4	5

Q4 - Quanto você precisa de um tratamento médico para levar sua vida diária?

nada	muito pouco	mais ou menos	bastante	extremamente
1	2	3	4	5

Q5 - O quanto você aproveita a sua vida?

nada	muito pouco	mais ou menos	bastante	extremamente
1	2	3	4	5

Q6 - Em que medida você acha que sua vida tem sentido?

nada	muito pouco	mais ou menos	bastante	extremamente
1	2	3	4	5

Q7 - O quanto você consegue se concentrar?

nada	muito pouco	mais ou menos	bastante	extremamente
1	2	3	4	5

Q8 - Quão seguro você se sente em sua vida diária?

nada	muito pouco	mais ou menos	bastante	extremamente
1	2	3	4	5

Q9 - Quão saudável é o seu ambiente físico (clima, barulho, poluição, atrativos)?

nada	muito pouco	mais ou menos	bastante	extremamente
1	2	3	4	5

As questões seguintes perguntam sobre o **quão completamente** você tem sentido ou é capaz de fazer certas coisas nestas duas ultimas semanas.

Q10 - Você tem energia suficiente para o seu dia a dia?

nada	muito pouco	médio	muito	completamente
1	2	3	4	5

Q11 - Você é capaz de aceitar sua aparência física?

nada	muito pouco	médio	muito	completamente
1	2	3	4	5

Q12- Você tem dinheiro suficiente para satisfazer suas necessidades?

nada	muito pouco	médio	muito	completamente
1	2	3	4	5

Q13 - Quão disponíveis estão para você as informações que precisa no seu dia a dia?

nada	muito pouco	médio	muito	completamente
1	2	3	4	5

Q14 - Em que medida você tem oportunidades de atividades de lazer?

nada	muito pouco	médio	muito	completamente
1	2	3	4	5

As questões seguintes perguntam sobre **quão bem ou satisfeito** você se sentiu a respeito de vários aspectos de sua vida nas últimas duas semanas.

Q15 - Quão bem você é capaz de se locomover?

muito ruim	ruim	nem ruim nem bom	bom	muito bom
1	2	3	4	5

Q16 - Quão satisfeito (a) você está com o seu sono?

muito insatisfeito	insatisfeito	nem satisfeito nem insatisfeito	satisfeito	muito satisfeito
1	2	3	4	5

Q17 - Quão satisfeito (a) você está com a sua capacidade de desempenhar as atividades do seu dia a dia?

muito insatisfeito	insatisfeito	nem satisfeito nem insatisfeito	satisfeito	muito satisfeito
1	2	3	4	5

Q18 - Quão satisfeito (a) você está com sua capacidade para o trabalho?

muito insatisfeito	insatisfeito	nem satisfeito nem insatisfeito	satisfeito	muito satisfeito
1	2	3	4	5

Q19 - Quão satisfeito(a) você está consigo mesmo?

muito insatisfeito	insatisfeito	nem satisfeito nem insatisfeito	satisfeito	muito satisfeito
1	2	3	4	5

Q20 - Quão satisfeito(a) você está com suas relações pessoais (amigos, parentes, conhecidos, colegas)?

muito insatisfeito	insatisfeito	nem satisfeito nem insatisfeito	satisfeito	muito satisfeito
1	2	3	4	5

Q21 - Quão satisfeito(a) você está com sua vida sexual?

muito insatisfeito	insatisfeito	nem satisfeito nem insatisfeito	satisfeito	muito satisfeito
1	2	3	4	5

Q22 - Quão satisfeito (a) você está com o apoio que recebe dos seus amigos?

muito insatisfeito	insatisfeito	nem satisfeito nem insatisfeito	satisfeito	muito satisfeito
1	2	3	4	5

Q23 - Quão satisfeito(a) você está com as condições do local onde mora?

muito insatisfeito	insatisfeito	nem satisfeito nem insatisfeito	satisfeito	muito satisfeito
1	2	3	4	5

Q24 - Quão satisfeito (a) você está com o seu acesso aos serviços de saúde?

muito insatisfeito	insatisfeito	nem satisfeito nem insatisfeito	satisfeito	muito satisfeito
1	2	3	4	5

Q25 - Quão satisfeito(a) você está com seu meio de transporte?

muito insatisfeito	insatisfeito	nem satisfeito nem insatisfeito	satisfeito	muito satisfeito
1	2	3	4	5

A questão seguinte refere-se a **com que frequência** você sentiu ou experimentou certas coisas nas últimas duas semanas.

Q26 - Com que frequência você tem sentimentos negativos, tais como mau humor, desespero, ansiedade, e depressão?

nunca	algumas vezes	frequentemente	muito frequentemente	sempre
1	2	3	4	5

7.4. Anexo 4 – Escalas para Graduação da Toxicidade Aguda

4.1 Toxicidade Aguda da Radioterapia Baseada na Escala de Graduação da (CTC) v 2.0

Toxicidade ginecológica	Grau 0	Grau 1	Grau 2	Grau3	Grau 4
Ondas de calor	ausente	leve ou não mais que uma por dia	moderado e mais que uma por dia	–	–
Dispareunia	ausente	dor leve não interferindo na função	dor moderada interferindo na atividade sexual	dor severa impedindo a atividade sexual	–
Libido	normal	diminuição do interesse	Perda severa do interesse	–	–
Secura vaginal	ausente	leve	Requer tratamento, ou interfere na função sexual	–	–

4.2 Toxicidade Aguda da Radioterapia Baseada na Escala de Graduação da RTOG

Toxicidade	Grau 0	Grau 1	Grau 2	Grau 3	Grau 4
Gastrintestinal baixo incluindo pélvis	Sem alterações	Aumento na Frequência ou característica do hábito intestinal, não requer medicação. Desconforto retal que não requer analgésico.	Diarreia que requer medicações. Dor retal ou abdominal que requer analgésico.	Diarreia que requer suporte parenteral. Grande quantidade de muco ou sangue requer fralda. Distensão de alça intestinal (através de RX)	Obstrução aguda ou subaguda, fístula ou perfuração; Sangramento gastrintestinal que requer transfusão. Dor abdominal ou tenesmo (sondagem ou derivação para descompressão)
Gastrintestinal alto	Sem alterações	Anorexia com perda do peso $\leq$ do que 5%. Náusea que não requer antiemético. Desconforto abdominal que não requer medicação.	Anorexia com perda de peso $\leq$ a 15%. Náusea e ou vômito que requer antiemético. Dor abdominal que requer analgésico.	Anorexia com perda de peso > que 15%, ou necessidade de sonda para alimentação. Náusea e / ou vômito que requer sonda ou suporte parenteral.Dor abdominal severa mesmo medicada. Hematemise ou melena. Distensão abdominal	Obstrução aguda ou subaguda de íleo, perfuração, sangramento gastrintestinal que requer transfusão.Dor abdominal que requer sonda para descompressão ou derivação intestinal.
Geniturinária	Sem alterações	Frequência urinária duas vezes maior que o hábito normal.Disúria ou urgência que não requer tratamento	Frequência urinária ou noctúria em intervalo maior que uma hora. Disúria espasmo vesical que requer anestésico local (pyridium).	Frequência com urgência e nuctúria a cada hora ou menos / disúria , dor em pélvis, ou espasmo vesical que requer regular frequente narcótico. Hematúria franca.	Hematúria que requer transfusão. Obstrução aguda de bexiga devido a coágulos.Ulceração ou necrose
Dermatológica	Sem alterações	Eritema folicular fraco ou apagado, epilação, descamação seca, diminuição da sudorese.	Eritema brando ou claro, descamação úmida em placas, edema moderado.	Descamação úmida confluente, além das dobras da pele, edema em "casca de laranja"	Ulceração, Hemorragia, necrose.
Hematológica WBC(X1000)	$\geq$ 4,0	3,0 - < 4,0	2,0 - <3,0	1,0 - <2,0	< 1,0
Plaquetas (X1000)	> 100	75 - < 100	50 - < 75	25 - <50	< 25 ou sangramento espontâneo
Neutrófilos	$\geq$ 1,9	1,5 - < 1,9	1,0 - <1,5	0,5 - <1,0	< 0,5 ou sepsis
Hemoglobina (GM %)	> 11	11-9,5	9,5-7,5	< 7,5 – 5,0	_
Hematócrito (%)	$\geq$ 32	28 - < 32	<28	Requer transfusão	_

7.5. Anexo 5 – Escala para Graduação de eventos adversos após a radioterapia

Eventos Adversos da Radioterapia Baseada na Escala de Graduação da (CTCAE) v 3.0

Eventos Adversos	Grau 1	Grau 2	Grau 3	Grau 4	Grau 5
Ondas de calor	Leve	Moderada	Interferindo na atividade diária (AD)	-	-
Dispareunia	Leve, não interfere na função sexual	Moderada: analgesia, interfere na função sexual	Itensa; analgesia: interferência intensa na função sexual	Impossibilita a função sexual	–
Libido	Diminuição do interesse, sem interferir no relacionamento; intervenção não indicada	Diminuição do interesse; interferência intensa no relacionamento; intervenção indicada	–	–	–
Secura vaginal	Leve	Interferindo na função sexual; dispareunia; intervenção indicada	–	–	–
Diarreia	Aumento <4 evacuções por dia; leve aumento na eleminação por ostoma	Aumento de 4-6 evacuações por dia ;hidratação indicada; moderado aumento na eliminação por ostomia; sem interferir na (AD)	Aumento≥ 7 evacuações por dia ; incontinencia; hidratação indicada; intenso aumento na eleminação por ostomia: interferindo na (AD)	Risco de vida, (colapso hemodinâmico)	Morte
Disúria	Leve não interferindo na (AD)	Moderada; analgesia interferindo na (AD)	Intenso; analgesia; interferindo intensamente na (AD)	Incapacitante	–
Sangramento	Leve; intervenção não indicada	Sintomático; intervenção médica ou cauterização indicada	Transfusão ; Intervenções (RX, cirúrgia , radioterapia RX) indicada	Risco de vida, intervenção urgente indicada	Morte
Incontinência urinária	Ocasional; não indicado uso de absorventes	Espontaneo; indicado uso de absorventes	Interferindo com (AD); intervenção indicada	Intervenção cirúrgica indicada	–
Dor	Leve não interferindo na função	Moderada interferindo na função	Intensa, interferindo intensamente na função	Incapacitante	–

7.6. Anexo 6 – Artigo da dissertação de mestrado

Arch Gynecol Obstet 2008; 278(3): 215-23.

Quality of Life and Acute Toxicity of Radiotherapy in Women with Gynecologic Cancer: a Prospective Longitudinal Study

Ana Francisca Vaz[a], Aarão Mendes Pinto-Neto[a,*], Délio Marques Conde[b], Lúcia Costa-Paiva[a], Sirlei Siani Morais[a], Sérgio Carlos Barros Esteves[a]

[a]Department of Gynecology and Obstetrics, Universidade Estadual de Campinas, Campinas, Brazil

[b]Department of Gynecology and Obstetrics, Universidade Federal de Goiás, Goiânia, Brazil

*Corresponding author: Department of Gynecology and Obstetrics, Universidade Estadual de Campinas. Rua Alexander Fleming, 101, Cidade Universitária ‘‘Zeferino Vaz’’, 13083-970, Campinas, SP, Brazil.

Phone/Fax: +55 19 3521 9306; E-mail address: aarao@unicamp.br

Abstract

Objective: To investigate the incidence of acute toxicity of radiotherapy, evaluate quality of life (QOL) and identify its predictors in a cohort of gynecologic cancer patients. **Methods:** A longitudinal prospective study was conducted including 107 women between the ages of 18 and 75 years with cervical or endometrial cancer. Acute toxicity was evaluated according to the Common Toxicity Criteria and the Radiotherapy Oncology Group toxicity criteria. QOL was measured with World Health Organization's Quality of Life instrument-Abbreviated version (WHOQOL-BREF) before and at completion of radiotherapy and during the first follow-up clinical visit. QOL scores were assessed by ANOVA for repeat measures. Percentage variation of QOL scores from the time before radiotherapy to the first clinical visit was compared with control variables by the Wilcoxon test. Multiple linear regression analysis was used to identify predictors of QOL. **Results**: Ninety-five women completed the three QOL assessments. The incidence of acute toxicity was 93.5% and the most common complaint was lower gastrointestinal (79.6%). A significant increase in QOL scores was observed in the physical and psychological domains, as well as general health and overall QOL. Upper gastrointestinal toxicity (p=0.043) and surgery (p=0.027) negatively affected general health, while improvement in vaginal bleeding (p=0.047) positively influenced general health. **Conclusions:** A high incidence of acute toxicity of radiotherapy was observed. At the completion of treatment, QOL improved in gynecologic cancer patients. Women with upper gastrointestinal toxicity and history of surgery are at risk for having a worse QOL.

Keywords: Quality of life; Gynecologic cancer; WHOQOL-BREF questionnaire; Radiotherapy; Side effects

Introduction

Gynecologic cancer is one of the most common groups of malignancies. Cervical cancer is the second most common cancer among women worldwide, occurring more frequently in developing countries [1]. In Brazil, 22,910 new cases of uterine cancer (cervix and corpus) are expected for the year 2006 [2]. Despite improvement in screening programs, diagnosis is still made in an advanced stage in a significant number of cases.

Treatment for late-stage cancer usually requires a combination of multiple modalities such as surgery, radiotherapy and chemotherapy. These therapies may produce side effects such as vaginal stenosis, changes in the bowels, bladder and ovarian function [3]. Sleep disturbances [4], ideation of suicide [5], menopausal symptoms and compromise of sexual functioning [6,7] were reported among women with gynecologic cancer. These complaints may contribute towards a negative perception of quality of life (QOL). Thus, QOL in these women may be affected both by the diagnosis and anti-neoplasm therapy [8].

The study on QOL became an important parameter in the evaluation of new treatments [8]. The definition of QOL is subjective because it encompasses the sociocultural aspects of the population studied and the individual's own perception of health status [9]. Previous studies have described QOL in women with gynecologic cancer [4-6, 8 10], suggesting that with time QOL suffers modifications [4, 6]. During active treatment QOL and mood may be impaired [4, 11, 12], which tend to improve over time [4, 6]. However, distortion of body image and sexuality problems may persist [6, 7]. Some possible predictors of QOL in women treated for gynecologic cancer include well-being [13], and performance status [8, 14] prior to treatment, cancer distress, reproductive concerns, maladaptive coping [15] and severity of surgery [8].

Regarding factors that may influence QOL in women with gynecologic cancer, it is worth bearing in mind the role of radiotherapy in the induction of acute and late toxicity. Acute side effects due to ionizing radiation may include anemia, leukopenia, changes in the skin, gastrointestinal and genitourinary tract, among

others [3]. Previous reports demonstrated a decline in overall well-being and QOL and increase in treatment-related symptoms during radiotherapy [11, 12, 16].

Overall, studies on QOL in gynecology cancer patients were conducted in developed countries with different social cultural realities, which may influence the perception of QOL. In addition, there is a paucity of information on QOL and acute toxicity of radiotherapy in cervical or endometrial cancer patients gained from longitudinal studies. Given these various considerations, we conducted the current study to investigate the incidence of acute toxicity of radiotherapy, to prospectively evaluate QOL, and identify its predictors in a cohort of women with gynecologic cancer.

Methods

Sample size

Sample size was calculated in at least 52 subjects, based on a previous study in which the frequency of acute toxicity of radiotherapy was 84% [17]. Calculation of the confidence interval for the incidence of acute toxicity was 95%, assuming a significance level of 5%. Sample size was calculated for a sampling error of 10%. This error represents the incidence variation to be found and determines the expected interval to find the incidence [18].

Subjects

Between March 2005 and March 2006, a longitudinal prospective study was conducted in the Women's Hospital, School of Medicine, Universidade Estadual de Campinas, Campinas, Brazil. Participants of this study were selected among patients consecutively treated in this hospital. Included in the study were women with cervical or endometrial cancer, between the ages of 18 and 75 years, who had undergone the entire treatment in the institution. Women with a history of pelvic radiation were ineligible. Of the 111 women selected, four of them refused to participate in the study, allegedly due to a lack of time. Thus, 107 women were included.

Assessment before radiotherapy included interview, clinical evaluation and complete blood count. Participants were interviewed to investigate sociodemographic and clinical characteristics, e.g. age, race/ethnicity, level of education, marital status, monthly family income, employment status, and menopausal status. Before radiotherapy and in the first follow-up visit, complaints of vaginal bleeding and pain were investigated by using a checklist. Disease- and treatment-related data were gathered from medical records: cancer site, surgery, chemotherapy, cancer stage according to the International Federation of Gynecology and Obstetrics (FIGO). This study was approved by the Institutional Review Board and all women signed an informed consent form.

Radiotherapy Procedure

Radiotherapy was performed with photon beam energy in a 10 MV megavoltage linear accelerator and a cobalt radiation therapy machine, using the four-field technique. For patients with anteroposterior diameter smaller than 17 cm, a parallel opposite field technique (anterior and posterior) was used. The total mean pelvic dose was 44.9 Gy (19.8-50.4Gy)/11-28 fractions, with a boost dose of 7.20-14.40 Gy in the parametria for stage IIB-IV (55 patients), in daily fractions of 1.8-2.0Gy for five days a week. For brachytherapy, 4-5 insertions were performed with a mean dose of 6.13 Gy (4-8Gy) in the nucletron-microselectron device with a radioactive iridium 192 source and weekly interval between insertions.

Evaluation of Acute Toxicity of Radiotherapy

On a weekly basis, one of the researchers prospectively assessed the incidence of acute toxicity of radiotherapy by performing a clinical evaluation and ordering a complete blood count. Acute toxicity was graded according to the National Cancer Institute Common Toxicity Criteria-version 2 (NCI CTC) [19] for hot flashes and the Radiotherapy Oncology Group (RTOG) Toxicity Criteria [20] for upper and lower gastrointestinal, genitourinary, skin and hematologic toxicity. Women who had previously undergone radiotherapy, had changes in complete blood count (e.g. anemia or leukopenia), or clinical complaint that might be

mistaken for acute side effects before beginning radiotherapy were excluded from the assessment of one type of toxicity. However, these women were included in the investigation of other types of toxicity.

Quality of Life Assessment

To assess QOL a questionnaire of the World Health Organization's Quality of Life instrument-abbreviated version was used (WHOQOL-BREF) [21]. WHOQOL-BREF is a generic instrument for assessment of QOL, which has already been translated and validated to the Portuguese language in Brazil [22]. It is a multidimensional questionnaire, composed of 26 items, with four domains: physical, psychological, social relationships and environment. There are also two questions for assessment of overall QOL and general health. Higher scores indicate a better QOL. QOL was assessed in the following three points in time (T): prior to the beginning of radiotherapy (T1), at completion of radiotherapy (T2) and during the first clinical follow-up visit 30 days after completion of radiotherapy (T3). QOL was studied using the patients as their own controls over time.

Statistical analysis

Results were presented as medians, means and standard deviations (SD) or as absolute and relative frequencies, according to the type of variable. To calculate the incidence of acute toxicity of radiotherapy all women recruited for the study were included, because all underwent at least part of the radiotherapy program. For assessment of QOL, only women who completed all three evaluations were taken into consideration.

QOL was assessed with time using variance analysis for repeat measures (ANOVA). Bivariate analysis was performed, calculating the mean percentage variation of QOL scores between the time before radiotherapy (T1) and the first clinical follow-up visit (T3). This variation was compared among control variables using the Wilcoxon test, identifying the factors associated with QOL. For multiple analyses, scores were transformed into $\log_{10}$. Multiple linear regression analysis was used with a stepwise variable selection method for identification of QOL

predictors, considering the domains and two questions from the WHOQOL-BREF questionnaire as dependent variables. For data analysis, the SAS program version 8.2 was used.

Results

The median age of the participants was 60 years (range 21-75 years). Four women died during radiation and two abandoned the treatment. However, these women had undergone radiotherapy apart from the program. After radiotherapy, one woman died and five did not attend the first clinical follow-up visit. Deaths were related to progression of the disease. Thus, 95 women completed the three QOL assessments. Treatment was not discontinued because of toxicity in any patient. Nineteen patients underwent chemotherapy.

The characteristics of participants are shown in Table 1. It was observed that most patients were 60 years or younger (51.4%), had cervical cancer and advanced stage (III-IV) uterine cancer (63.5%). Most women were categorized as non-white (54.2%), reported a lower income (75.7%), low level of education (77.6%), were homemakers (58.8%) and were in the postmenopause (82.2%). Almost half of the participants referred living with a partner (50.5%). A smaller proportion of women had undergone surgery (37.4%). Vaginal bleeding and pain were reported by 35.5% and 48.6% of women, respectively.

In Table 2 are the incidence and grade of acute toxicity of radiotherapy. Eighty-nine women (83.2%) underwent external radiotherapy and brachytherapy, eight underwent only external radiotherapy and 10 only brachytherapy. Some grade of acute radiotherapy reaction occurred in 100 women (93.5%). The most common toxicities occurred in the lower gastrointestinal tract in 79.6%, genitourinary tract in 74.5% and upper gastrointestinal tract in 70.4%. The least frequent toxicities were hot flashes and hematocrit changes in 23.5% and 20.5%, respectively. Almost all toxicities were grade 1 and 2 (96.3%). Four women (3.7%) had grade 3 toxicity; three of these had skin abnormalities and one had an altered hemoglobin level. No grade 4 toxicity was found.

Table 3 shows a global picture of QOL in different times, considering domains and questions regarding general health and overall QOL of the WHOQOL-BREF questionnaire. Prior to initiation of radiotherapy, the best QOL score was observed in the social relationship domain (77.0±12.7), which was maintained in the following evaluations, while the lowest score was observed in questions relating to general health (58.7±23.6) and environment domain (62.8±11.1). At completion of radiotherapy, the lowest score was observed in the environment domain (64.7±10.8). In the first clinical follow-up visit, general health had the highest increase in score (76.3±20.1), although it remained below the average score for the social relationship domain (80.8±12.7). Despite elevation of all QOL scores, ANOVA identified that these alterations were significant for the physical ($p=0.0052$) and psychological ($p<0.0001$) domains and for overall QOL ($p=0.0006$) and general health ($p<0.0001$).

In Table 4 are factors that presented a significant percentage variation in QOL scores, carrying out bivariate analysis. For the physical domain, a significant variation was identified for pain improvement ($p=0.012$), premenopausal status ($p=0.022$) and having a partner ($p=0.007$), while pain improvement was the only factor identified ($p=0.047$) for the social relationships domain. For environment domain, absence of upper gastrointestinal toxicity ($p=0.005$), pain improvement ($p=0.012$) and premenopausal status ($p=0.010$) had significant percentage increase. For general health, the factors identified were absence of upper gastrointestinal toxicity ($p=0.023$), no surgery ($p=0.001$), stage III-IV ($p=0.006$), cervical cancer ($p=0.012$), improvement in vaginal bleeding ($p=0.001$) and premenopausal status ($p=0.030$). No factor was associated with an increase in the psychological domain and overall QOL scores.

Table 5 shows the results of multiple linear regression analysis for general health. It was observed that upper gastrointestinal toxicity ($p=0.043$) and history of surgery ($p=0.027$) negatively affected QOL, while improvement in vaginal bleeding positively influenced QOL ($p=0.047$). A significant predictor was not identified for overall QOL, as well as the physical, psychological, social relationships and environment domains.

Discussion

In this prospective longitudinal study, the aims were to investigate the incidence of acute toxicity of radiotherapy, prospectively evaluate QOL and identify its predictors in a cohort of women with gynecologic cancer. Overall, a high incidence of toxicity during irradiation was observed, as well as improvement in QOL after therapy.

The high incidence of acute radiation-induced toxicity in the present cohort is consistent with that reported by other authors [17, 23]. However, Weiss et al. [24] in a retrospective study reported a 65.4% frequency of acute toxicity in women with gynecologic cancer, more commonly a low-grade toxicity. The occurrence of acute side effects described by those authors was elevated, although lower than that observed in the present cohort. A predominance of low-grade toxicity also occurred in the present study, confirming previous findings [23, 25]. This possibly explains the fact that treatment discontinuation did not occur.

The most common acute reactions occurred in the gastrointestinal and genitourinary tracts. These findings are consistent with previous studies describing that these toxicities were more frequent in women with gynecologic cancer undergoing radiotherapy [12, 14, 17, 24, 25]. More recently, in a prospective study with uterine cancer patients, Caffo et al. [12] reported that gastrointestinal symptoms were the most common complaints. Gastrointestinal radiation-induced toxicity may include increased stool frequency, fecal fat excretion and decreased absorption of bile acid [26]. The majority of these changes improve with time, but some may persist for the long term [25]. Following gastrointestinal symptoms, genitourinary symptoms (dysuria, pollakiuria, urgency) were the most frequent complaints. In line with our results, other authors observed a similar picture [17, 24, 25].

Differences observed between our findings and those described in previous studies may be related to diverse factors, highlighting a retrospective design of several studies, differences in radiotherapy schedules and doses, use of different assessment criteria for acute toxicity and report of only severe acute morbidity. It is possible that the rate of mild treatment-related symptoms is underreported in

studies, since these symptoms are subject to personal interpretation and interobserver variations [25].

Despite the high incidence of acute toxicity, QOL improved on completion of radiotherapy. Baseline assessments showed that question on general health and environment domain had lower QOL scores. The question on general health assesses self-perception of health status. Our data suggest that before radiotherapy women expressed deeper dissatisfaction with their health. It is possible that the diagnosis of uterine cancer, information that radiotherapy is required, uncertainties and expectations about treatment outcomes and cancer-related symptoms negatively influence their perception of health.

In contrast to many QOL instruments, the WHOQOL-BREF questionnaire includes an environment domain, in which financial resources, transport, access to health services and new information are assessed, among other aspects. Therefore, the environment plays an important role in determining health status, limiting or facilitating access to these services [26]. It is worth mentioning that the institution conducting this study is a public health service, managing women of low income and little education. Therefore, the financial difficulties of the socially disadvantaged may delay access to health services and information about the disease. This fact may have negatively influenced QOL.

In this study, QOL improved over time with significant modifications in the physical and psychological domains, and in questions concerning general health and overall QOL. Consistent with our results, previous studies have reported improvement in the physical domain [11, 8] and psychological aspects in women with gynecologic cancer after treatment [10, 11]. Bye et al. [11] reported worsening in physical functioning among gynecologic (cervix, edometrium) cancer patients during radiotherapy, occurring improvement in the follow-up period. However, the majority of those patients were hospitalized for treatment. In contrast, study participants were treated as outpatients, allowing them to do daily activities and reducing the repercussions of radiation on the physical domain. Another possible explanation for improvement in physical status is related to improvement in cancer-related symptoms after radiotherapy. This may reflect success in the

treatment for local disease control. It is worth mentioning that during radiotherapy, these women received information about the disease, treatment and possible side effects. Improvement in psychological symptoms may reflect the multidisciplinary care offered to patients, highlighting psychological support. Knowledge of side effects, along with psychological support may lead to a positive perception of QOL, minimizing the impact of radiotherapy. Other authors have emphasized the importance of providing patients [5,10-12] and their partners [28] whit psychosocial support and information on treatment.

Following increasing scores in the physical and psychological domains, there was an improvement in general health and overall QOL. These two questions evaluate the woman's subjective impression of her health and QOL. It is possible that physical symptom relief, treatment outcome with a subjective perspective of a cure and support offered in the institution contributed towards a more positive evaluation of health status and QOL on completion of radiotherapy. Other authors described a positive correlation between QOL scales, indicating that improvement in a certain scale is followed by improvement in other scales and overall QOL [10].

Chan et al. [10] conducted a prospective study among Chinese women with gynecologic cancer (cervix, corpus, ovary, and vulva) and a median age of 49.5 years. Applying a cancer-specific QOL instrument, these authors reported that improvements in different functional scales and symptom relief were followed by an improvement in QOL. In this case study, bivariate analysis indicated that relief of symptoms was also associated with a positive percentage variation in QOL scores. Pain relief was associated with significant percentage increase in QOL scores for the physical, social relationship and environment domains, while improvement in vaginal bleeding was related to increase in general health score. These data suggest an interrelationship between different factors that may influence QOL and its impact on subjective health evaluation. Confirming our findings, other authors identified an inverse correlation between symptoms and QOL [5, 10]. Ell et al. [5] conducted a study to evaluate predominantly low-income Latin women with gynecologic (cervix , endometrium, and ovary) or breast cancer. These authors demonstrated that pain was associated with depression. Furthermore,

women with depressive symptoms were more likely to report poorer physical and functional status, as well as poorer social and emotional well-being. These data indicate an interrelationship between physical and psychological symptoms and their possible repercussions on QOL.

In the present cohort, other factors showed a significant increase in QOL scores compared to initial assessment. The relationship of these factors with QOL has been underreported in previous studies. Baseline cervical cancer, advanced stage, and premenopausal status showed low scores. It is possible that before radiotherapy the impact of diagnosis and cancer-related symptoms was greater in these conditions. During follow-up, these factors were associated with a significant increase in QOL scores. Data suggests that a worse QOL is observed before the start of radiotherapy. Furthermore, the more symptomatic are gynecologic cancer patients, the more these women will benifit from treatment, as observed by both symptom relief and QOL improvement. Therefore, in longitudinal studies, we need to consider the health conditions in women prior to treatment [8], since pretreatment factors may significantly influence QOL in cancer patients [29]. Other authors have described some differences in QOL according to staging and cancer site that tended to disappear in the long term [8, 10].

On multivariate analysis, predictors of improvement in QOL were absence of upper gastrointestinal toxicity, history of surgery and improvement in vaginal bleeding. Results of the analysis demonstrated the importance of symptoms in the perception of QOL, since these factors remained significant only regarding general health. Bye et al. [11] in a prospective study described a worse QOL in women with acute gastrointestinal symptoms, confirming our findings. Morbidity that is associated with surgery may negatively influence QOL. Abdominal surgery may be perceived as a factor that negatively affects health because it can determine physical limitations and psychological distress. Other authors reported an association between severity [8] or extent [30] of surgery and worse QOL. However, these findings need to be confirmed in prospective studies designed specifically to investigate such a relation.

For the interpretation of our data, it is worth keeping in mind several aspects. A generic QOL questionnaire was used. It may fail to assess specific domains that may affect QOL in women with gynecologic cancer, such as sexual functioning. However, this domain may also not be adequately measured by cancer-specific instruments [31]. Although the WHOQOL-BREF is a generic tool, it has permitted the identification of factors that negatively affect QOL in women with gynecologic cancer. Previous studies have also applied the WHOQOL-BREF questionnaire to assess QOL in gynecologic cancer patients [32, 33]. To our knowledge, no site or cancer-specific tool have been translated and validated to the Portuguese language in Brazil, so its use has been precluded. Future studies should evaluate the psychosocial repercussions of gynecologic cancer on male partners, since they may express concern about the diagnosis, prognosis, and sexuality [28].

In the present study, we highlighted the use of a QOL questionnaire that was internationally standardized and validated, as well as a widely used toxicity criteria. We would also like to emphasize that QOL was evaluated using the participants as their controls over time. Contrary to cross-sectional studies, a prospective longitudinal design permitted us to draw causal inferences. A longitudinal study allowed us to make a more accurate assessment of the incidence of acute toxicity that is usually underreported. The importance of investigating acute side effects of radiotherapy is based on several aspects. Knowledge of the frequency of these effects may offer patients more appropriate clinical care. As reported in the current study, acute toxicity may negatively affect QOL. It is worth remembering that acute side effects are one of the main risk factors for late complication [25]. It is possible that this was one of the first studies in Latin America to report the incidence of acute toxicity of radiotherapy and QOL in women with gynecologic cancer.

In conclusion, we believe that our results are of interest to health professionals involved in the management of gynecologic cancer patients. At completion of radiotherapy, these women showed an elevated incidence of acute toxicity of radiotherapy and improvement in QOL. QOL was significantly improved in patients who presented no upper gastrointestinal toxicity, reported improvement in vaginal bleeding and had not undergone surgery. Future research should use cancer or

site-specific and generic questionnaires, as well as tools to evaluate other factors, e.g. performance status, sexuality, relationship between the couple and determine its impact on QOL in women with gynecologic cancer.

Acknowledgments Our sincere thanks to professor Elfriede R. Greimel, Medical University of Graz, for her valuable comments during the revision of this manuscript and for providing us whit the necessary motivation for its publication.

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Table 1 – Sociodemographic and clinical characteristics of women with gynecologic cancer (N=107)

Characteristics	n (%)
Age (years)	
≤60	55 (51.4)
>60	52 (48.6)
Cancer site	
Cervix	68 (63.5)
Endometrium	39 (36.5)
FIGO Stage	
I	31 (29.0)
II	8 (7.5)
III	62 (57.9)
IV	6 (5.6)
Race/ethnicity	
White	49 (45.8)
Non-white	58 (54.2)
Education (years)	
≤4	83 (77.6)
>4	24 (22.4)
Marital status	
Without partner	53 (49.5)
With partner	54 (50.5)
Family income per month (US$)	
≤484	81 (75.7)
>484	26 (24.3)
Employment status	
Employed	22 (20.6)
Unemployed	22 (20.6)
Homemaker	63 (58.8)
Menopausal status	
Premenopause	19 (17.8)
Postmenopause	88 (82.2)
Surgery	
Yes	40 (37.4)
No	67 (62.6)
Vaginal bleeding	
Yes	38 (35.5)
No	69 (64.5)
Pain	
Yes	52 (48.6)
No	55 (51.4)

Table 2 – Incidence and grade of acute toxicity of radiotherapy in women with gynecologic cancer (N=107)

Acute Toxicity	Grade	ERT[a]	BRT[a]	ERT and BRT[a]	$N_{toxicity}/N_{evaluated}$[b] (%)
Lower gastrointestinal		(N=8)*	(N=9)*	(N=86)*	82/103 (79.6)
	1	3 (37.5)	2 (22.2)	20 (23.3)	
	2	2 (25.0)	0	55 (64.0)	
Genitourinary		(N=7)*	(N=8)*	(N=83)*	73/98 (74.5)
	1	1 (14.3)	1 (12.5)	22 (26.5)	
	2	5 (71.4)	2 (25.0)	42 (50.6)	
Upper gastrointestinal		(N=7)*	(N=8)*	(N=83)*	69/98 (70.4)
	1	2 (28.6)	2 (25.0)	32 (38.6)	
	2	3 (42.9)	0	30 (36.1)	
Skin		(N=8)	(N=10)	(N=89)	37/107 (34.6)
	1	3 (37.5)	–	24 (27.0)	
	2	1 (12.5)	–	6 (6.7)	
	3	1 (12.5)	–	2 (2.2)	
Hot flashes		(N=7)*	(N=9)*	(N=65)*	19/81 (23.5)
	1	2 (28.6)	1 (11.1)	7 (10.8)	
	2	0	1 (11.1)	8 (12.3)	
Leukocytes		(N=8)	(N=9)*	(N=88)*	42/105 (40.0)
	1	0	1 (11.1)	29 (33.0)	
	2	0	0	12 (13.6)	
Hemoglobin		(N=2)*	(N=9)*	(N=71)*	24/82 (29.3)
	1	1 (50.0)	0	19 (26.8)	
	2	0	0	3 (4.2)	
	3	0	0	1 (1.4)	
Hematocrit		(N=7)*	(N=9)*	(N=88)*	18/88 (20.5)
	1	1 (25.0)	0	14 (18.7)	
	2	1 (25.0)	0	2 (2.7)	

[a]Eight women underwent external radiotherapy (ERT), 10 brachytherapy (BRT) and 89 external radiotherapy and brachytherapy.

$N_{toxicity}$: number of women with toxicity; $N_{evaluated}$[b]: number of women included in the investigation of toxicity rate.

*Number of women evaluated for each type of toxicity. Some women with symptoms or changes in complete blood count prior to treatment were excluded from the assessment of one type of toxicity, but were included in the assessment of other types.

Table 3 – Comparison of mean scores of quality of life in women with gynecologic cancer, before (T1), at completion of radiotherapy (T2) and in the first follow-up visit to the clinic (T3) (N=95)

WHOQOL-BREF	Mean (SD)			ANOVA[a]	p-value[b]		
	T1	T2	T3		T1vsT2	T1vsT3	T2vsT3
Physical	63.7 (17.7)	67.8 (13.7)	70.3 (15.6)	0.0052	0.0120	0.0002	NS
Psychological	65.8 (13.9)	70.8 (11.4)	70.4 (14.2)	<0.0001	0.0002	0.0004	NS
Social relationships	77.0 (12.7)	81.5 (11.9)	80.8 (12.7)	NS	NS	NS	NS
Environment	62.8 (11.1)	64.7 (10.8)	65.4 (11.7)	NS	NS	NS	NS
Overall quality of life	65.5 (17.2)	72.6 (13.7)	74.2 (16.5)	0.0006	<0.0016	0.0002	NS
General health	58.7 (23.6)	75.5 (14.6)	76.3 (20.1)	<0.0001	<0.0001	<0.0001	NS

[a]Friedman ANOVA for repeat measurements. [b]Wilcoxon Test for longitudinal samples.

NS: not significant.

Table 4 – Factors with significant percentage variation in quality of life scores in women with gynecologic cancer prior to radiotherapy (T1) and first clinical follow-up visit (T3)

Variables	Mean (SD)			p-value[a]
	T1	T3	% Variation	
Physical				
Pain				0.012
Improvement	59.1 (16.9)	88.5 (13.2)	49.7 (116.5)	
Others[b]	65.2 (17.7)	73.9 (16.2)	13.4 (41.7)	
Menopausal status				0.022
Postmenopause	64.3 (16.3)	72.4 (15.8)	12.7 (39.4)	
Premenopause	57.0 (23.8)	97.4 (13.2)	71.0 (139.5)	
Marital status				0.007
With Partner	61.5 (20.9)	83.6 (14.0)	35.9 (87.4)	
Without Partner	64.4 (14.3)	68.6(17.1)	6.4 (33.6)	
Social relationships				
Pain				
Improvement	74.3 (12.7)	84.1 (13.6)	13.2 (21.5)	0.047
Others[b]	77.9 (12.6)	81.6 (12.4)	4.7 (18.6)	
Environment				
Upper Gastrointestinal Toxicity				0.005
Yes	64.6 (8.5)	62.7 (12.2)	-2.8 (18.4)	
No	62.8 (11.8)	68.2 (11.5)	8.7 (18.1)	
Pain				0.012
Improvement	58.6 (11.4)	67.5 (12.3)	15.2 (20.1)	
Others[b]	64.3 (10.7)	65.8 (11.6)	2.4 (16.9)	
Menopausal status				0.010
Postmenopause	63.6 (10.7)	65.6 (12.0)	3.1 (16.9)	
Premenopause	60.7 (11.9)	71.8 (10.1)	18.3 (21.4)	
General health				
Upper Gastrointestinal Toxicity				0.023
Yes	64.7 (19.5)	75.4 (24.7)	16.7 (52.0)	
No	54.7 (24.4)	90.6 (18.0)	65.6 (92.4)	
Surgery				0.001
Yes	70.6 (17.8)	79.5 (21.2)	12.6 (42.4)	
No	48.9 (23.6)	85.7 (19.5)	75.3 (93.5)	
FIGO Stage				0.006
I-II	65.0 (23.2)	84.7 (21.3)	30.3 (75.9)	
III-IV	52.2 (23.3)	85.8 (19.4)	64.2 (85.4)	
Cancer site				0.012
Cervix	52.6 (24.1)	77.54 (19.53)	62.9 (84.9)	
Endometrium	64.7 (22.0)	74.31 (21.12)	30.6 (76.9)	
Vaginal bleeding				0.001
Improvement	45.2 (23.6)	84.2 (21.8)	86.2 (83.5)	
Others[b]	65.2 (20.7)	87.4 (19.4)	34.1 (78.1)	
Menopausal status				0.030
Postmenopause	59.7 (22.6)	84.0 (20.6)	40.8 (73.9)	
Premenopause	44.7 (27.1)	89.5 (17.1)	100.0 (109.7)	

Bivariate Analysis (N=95). [a]Wilcoxon Test. [b]Included in this category were women who did not have this symptom before radiotherapy and those who reported no improvement in symptom during follow-up.

Table 5 – Significant predictors of quality of life in women with gynecologic cancer. Multivariate Analysis* (N=95)

Variables	**Estimated Parameter**	**Standard error**	**p-value**	**R^2**
Upper Gastrointestinal Toxicity (yes vs no)	-33.54	18.80	0.043	0.039
Surgery (yes vs no)	-46.85	20.73	0.027	0.146
Vaginal bleeding (improvement vs others)	26.73	21.40	0.047	0.016

Variables included in the analysis: Age, cancer site, cancer stage, race/ethnicity, education, marital status, family income, employment status, menopausal status, surgery, chemotherapy, vaginal bleeding, pain, upper and lower gastrointestinal toxicity, genitourinary, skin, hot flashes, leukocytes, hemoglobin, hematocrit.

*R^2: 0.201; $p<0.0004$.

8. Apêndice

8.1. Trabalhos apresentados em congressos publicados em anais

8.1.1. Internacional

8.1.1. Ana Francisca Vaz, Aarão M. Pinto-Neto, MD, PhD, Délio Marques Conde, MD, PhD, Lúcia Costa-Paiva, MD, PhD, Sirlei Siani Morais, Adriana O. Pedro, MD, PhD, Sérgio Barros Esteves MD- Quality of life and prevalence of climateric and sexual symptoms after radiotherapy in women with gynecologic cancer: a prospective cohort study. Pôster apresentado no 20th Annual Meeting NAMS - Menopause: A New Experience: Bringing Technology to Menopausal Health, realizado em San Diego, USA, de 30 de setembro a 3 de outubro de 2009. Abstract Book, LB-20.

8.1.2. Nacional

8.2.1. VAZ AF, PINTO-NETO AM, CONDE DM, COSTA-PAIVA L, MORAIS SS, ESTEVES SB. Qualidade de vida de mulheres com câncer ginecológico: fatores asssociado. Pôster apresentado no I Congresso Brasileiro de Qualidade de Vida da Àrea de Saúde, promovido pelo Ministério da Educação do Brasil e Escola Paulista de Medicina da Universidade Federal de São Paulo – UNIFESP, REALIZADO EM São Paulo, SP, de 23 a 25 de março de 2007.

8.2.2. VAZ AF, PINTO-NETO AM, CONDE DM, COSTA-PAIVA L, MORAIS SS, ESTEVES SB. Qualidade de vida de mulheres com câncer ginecológico: fatores asssociado. Trabalho apresentado durante a 33ª Jornada Goiania de Ginecologia e Obstetrícia, promovida pela Federação de Brasileira das Associações de Ginecologia e Obstetrícia, realizada em Goiânia, GO, de 15 a 18 de agosto de 2007.

8.2.3. VAZ AF, PINTO-NETO AM, CONDE DM, COSTA-PAIVA L, MORAIS SS, ESTEVES SB. Qualidade de vida de mulheres com câncer ginecológico: fatores asssociado. Pôster apresentado durante o IX Congresso da Sociedade Brasileira de Radioterapia, VII Jornada de Física Médica, V Encontro de Enfermeiros Oncologistas em Radioterapia e IV Encontro de Técnicos de Radioterapia da SBRT, no Hotel Serrano – Gramado – RS, de período de 5 a 8 de setembro de 2007.

8.2.4. VAZ AF, PINTO-NETO AM, CONDE DM, COSTA-PAIVA L, MORAIS SS, ESTEVES SB. Qualidade de vida e efeitos adversos após a radioterapia em mulheres com câncer ginecológico: Um estudo de coorte prospectivo. Pôster apresentado durante o XI Congresso da Sociedade Brasileira de Radioterapia, IX Jornada de Física Médica, VII Encontro de Enfermeiros Oncologistas em Radioterapia e VI Encontro de Técnicos de Radioterapia da SBRT, realizado em Florianópolis – SC, de 2 a 5 de setembro de 2009.

8.2.5. VAZ AF, PINTO-NETO AM, CONDE DM, COSTA-PAIVA L, PEDRO A, MORAIS SS, ESTEVES SB. Qualidade de vida, sintomas climatéricos e sexuais em mulheres com câncer ginecológico: um estudo de coorte. Aceito para apresentação em pôster e selecionado para apresentação oral no XV Congresso Paulista de Obstetricia e Ginecologia, promovido pela Sociedade de Obstetricia e Ginecologia do Estado de São Paulo – SOGESP, realizado em São Paulo, de 2 a 4 de setembro de 2010. Programa Oficial, Codigo: 627, Sigla 52

8.2.6. VAZ AF, PINTO-NETO AM, CONDE DM, COSTA-PAIVA L, PEDRO A, MORAIS SS, ESTEVES SB. Qualidade de vida, sintomas climatéricos e sexuais em mulheres com câncer ginecológico: um estudo de coorte. Aceito para apresentação em pôster e selecionado para apresentação oral no XII Congresso da Sociedade Brasileira de Radioterapia, X Jornada de Física Médica, VIII Encontro de Enfermeiros Oncologistas em Radioterapia e VII Encontro de Técnicos de Radioterapia da SBRT, realizado em Campinas – SP, de 20 a 23 de outubro de 2010.