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Avaliação de Pacientes com Carcinoma de Colo Uterino Inicial Tratadas com Histerectomia Radical por Laparoscopia ou Laparotomia – Um Ensaio Clínico Randomizado

Porto Alegre
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Tese submetida ao Programa de Pós-Graduação em Ciências da Saúde da Fundação Universidade Federal de Ciências da Saúde de Porto Alegre como requisito para a obtenção do grau de Doutor.

Orientador: Prof. Dr. Antonio Nocchi Kalil

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No te quedes inmóvil
al borde del camino
no congeles el júbilo
no quieras con desgana
no te salves ahora
ni nunca
no te salves
no te llenes de calma
no reserves del mundo
sólo un rincón tranquilo
no dejes caer los párpados
pesados como juicios
no te quedes sin labios
no te duermas sin sueño
no te pienses sin sangre
no te juzgues sin tiempo

pero si
pese a todo
no puedes evitarlo
y congelas el júbilo
y quieres con desgana
y te salvas ahora
y te llenas de calma
y reservas del mundo
sólo un rincón tranquilo
y dejas caer los párpados
pesados como juicios
y te secas sin labios
y te duermes sin sueño
y te piensas sin sangre
y te juzgas sin tiempo
y te quedas inmóvil
al borde del camino
y te salvas
entonces
no te quedes conmigo.

Mario Benedetti

RESUMO

O carcinoma de colo uterino é uma doença de morbidade e mortalidade consideráveis. Aproximadamente 500 mil mulheres desenvolvem carcinoma de colo uterino a cada ano no mundo, sendo que 83% dos casos ocorrem nos países em desenvolvimento. Os objetivos deste estudo são comparar dor pós-operatória, taxa de complicações cirúrgicas perioperatórias, sobrevida global e sobrevida livre de doença em cinco anos entre pacientes submetidas à histerectomia radical laparoscópica e à histerectomia radical abdominal para tratamento do carcinoma de colo uterino em estádio inicial. Foram incluídas pacientes nos estádios IA2 com invasão linfovascular, IB e IIA estadiadas clinicamente com os critérios da Federação Internacional de Ginecologia e Obstetrícia e que foram randomizadas para serem submetidas à histerectomia radical laparoscópica (16) ou à histerectomia radical abdominal (14). Ambas as técnicas foram realizadas pela mesma equipe cirúrgica. A intensidade da dor pós-operatória pela Escala Verbal Numérica foi considerada o desfecho principal. A dor pós-operatória foi avaliada pela equipe de enfermagem, a cada seis horas, durante o cuidado pós-operatório usual. Não houve diferença nas características demográficas e no tempo cirúrgico, tipo histológico e número de linfonodos excisados entre grupos. A média dos escores de dor das pacientes submetidas à histerectomia radical laparoscópica foi significativamente menor que a média dos escores de dor das pacientes submetidas à histerectomia radical aberta em 36h de observação (p = 0,044) – a média da diferença entre os escores de dor foi de 1,42 pontos (IC 95%; 0,04 a 2,80). Quatro pacientes (25%) no grupo que realizou histerectomia radical laparoscópica e cinco pacientes (35,71%) no grupo que realizou histerectomia radical abdominal apresentaram complicações transoperatórias ou complicações pós-operatórias severas. Todas as complicações transoperatórias ocorreram no grupo que foi submetido à abordagem laparoscópica. O Risco Relativo de apresentar complicações foi RR: 0,70 (IC 95%; 0,23 a 2,11; p = 0,694). Três pacientes no grupo submetido à abordagem laparoscópica (18,8%) e três pacientes no grupo submetido à abordagem abdominal (21,4%) apresentaram linfonodos pélvicos comprometidos e receberam radioterapia adjuvante (p = 1,00). O tempo médio de seguimento foi de 83,26 meses (IC 95%; 69,22 a 97,3). O tempo médio de sobrevida global foi de 74,74 meses (IC 95%; 54,15 a 95,33) para as pacientes submetidas à abordagem laparoscópica e 91,67 meses (IC 95%; 74,97 a

108,36) para as pacientes submetidas à abordagem abdominal (teste de log-rank = 0,300). O tempo médio de sobrevida livre de doença foi de 81,07 meses (IC 95%: 60,95 a 101,18) para o grupo submetido à abordagem laparoscópica e 95,82 meses (IC 95%; 80,18 a 111,47) para o grupo submetido à abordagem abdominal (teste de log-rank = 0,37). A *hazard ratio* (HR – razão de dano) para sobrevida global foi de 2,05 (IC 95%; 0,51 a 8,24) e a HR para sobrevida livre de doença foi de 2,13 (IC 95%; 0,39 a 11,7). Concluímos que a histerectomia radical laparoscópica apresentou menores escores de dor pós-operatória em 36 horas de pós-operatório de maneira estatisticamente significativa e apresentou uma taxa de complicações similar à da histerectomia radical abdominal. Não houve diferença estatisticamente significativa na sobrevida e sobrevida livre de doença em cinco anos entre os dois grupos. Os achados deste estudo sugerem que a histerectomia radical laparoscópica é oncologicamente segura, e a menor dor pós-operatória favorece a escolha da histerectomia radical laparoscópica para o tratamento do carcinoma de colo uterino inicial.

Palavras-chave: Carcinoma de colo uterino. Laparoscopia. Histerectomia radical. Dor pós-operatória. Sobrevida.

ABSTRACT

Cervical cancer has considerable morbidity and mortality. Over 500,000 women have incident cervical cancer every year and 83% of cases occur in developing countries. This study aims to compare postoperative pain measured by Numeric Rating Scale, transoperative and postoperative complication; 5-year overall and disease-free survival for patients that underwent laparoscopic radical hysterectomy and abdominal radical hysterectomy for early cervical cancer. Clinically staged patients as IA2 with lymph vascular invasion, and IIA according to Federation International of Gynecology and Obstetrics were randomised to undergo laparoscopic radical hysterectomy (16) and abdominal radical hysterectomy (14). Both techniques were performed by the same surgical team. Postoperative pain measured by Numeric Rating Scale was the primary endpoint. Postoperative pain was assessed every six hours during usual postoperative care. Demographic profile, surgical time and histopathologic type and number of pelvic lymph nodes were similar for both groups. Laparoscopic radical hysterectomy group mean pain score was significantly lower than ARH in 36 hs of observation (1.42 95% CI: 0.04-2.80) (p = 0.044). Four patients (25%) in the group that underwent laparoscopic radical hysterectomy and 5 patients (35.71%) in the group that underwent abdominal radical hysterectomy presented transoperative or severe postoperative complication. All transoperative complication took place in the laparoscopic radical hysterectomy group. The Relative Risk for presenting complication was RR: 0.70 IC 95% (0.23 a 2.11); p=0.694. Three patients in the group that underwent laparoscopic radical hysterectomy (18.8%) and three patients in the group that underwent abdominal radical hysterectomy (21.4%) presented positive pelvic lymph nodes and received adjuvant radiotherapy. (p=1.00). Follow-up time was 83.26 months (CI 95%: 69.22 to 97.3). Mean overall survival time was 74.74 months (CI 95% 54.15 to 95.33) for patients that underwent laparoscopic radical hysterectomy and 91.67 months (CI 95% 74.97-108.37) for patients that underwent abdominal radical hysterectomy. (log-rank=0.30). Disease-free survival time was 81.07 months (CI 95%:60.95-101.19) for patients that underwent laparoscopic radical hysterectomy and 95.82 months (CI 95%: 80.18 a 111.47) for patients that underwent abdominal radical hysterectomy (log-rank test= 0.37) The overall hazard ratio was 2.05 (CI 95%: 0.51 to 8.24) and disease-free hazard ratio was 2.13 (CI 95%:0.39-11.7). Laparoscopic radical hysterectomy group mean pain

score was significantly lower than ARH in 36 hs of observation (mean difference score 1.42 95% CI: 0.04-2.80) (p=0.044) and has similar complication rate compared to abdominal radical hysterectomy. Laparoscopic and Abdominal Radical Hysterectomy had similar overall and disease-free survival in five years of follow-up. These findings suggest that laparoscopic radical hysterectomy is oncologically safe and the lower postoperative pain scores favour laparoscopic radical hysterectomy for treatment of early cervical cancer.

Key Words: Cervical cancer. Laparoscopy. Radical hysterectomy. Postoperative pain. Survival.

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LISTA DE ABREVIATURAS E SIGLAS

DNA: ácido desoxirribonucleico

EORTC-GCG: Organização Europeia para Pesquisa e Tratamento do Câncer – Grupo de Câncer Ginecológico

EORTC-QLQ: European Organization for Research and Treatment of Cancer – Quality of Life Questionaire

EVA: Escala Visual Analógica

EVN: Escala Verbal Numérica

FDG-PET: Tomografia por Emissão de Pósitrons com [18F] flurodeoxiglicose

FIGO: Federação International de Ginecologia e Obstetrícia

HPV: Papilomavirus Humano

HR: *hazard ratio* (razão de danos)

HRA: Histerectomia Radical Abdominal

HRL: Histerectomia Radical Laparoscópica

HRVLA: Histerectomia Radical Laparoscopicamente Assistida

IC 95%: intervalo de confiança de 95%

IELV: invasão do espaço linfovascular

IMC: Índice de Massa Corporal

INCA: Instituto Nacional do Câncer

NIC3: neoplasia intraepitelial de grau 3

OR: *odds ratio* (razão de chances)

p53: proteína 53

PET-TC : tomografia por emissão de pósitrons

pRB: proteína do retinoblastoma

RNM: ressonância nuclear magnética

RR: risco relativo

TC: tomografia computadorizada

TVP/EP: trombose venosa profunda/ embolia pulmonar

VS: *versus*

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1 INTRODUÇÃO

O carcinoma de colo uterino é uma doença de morbidade e mortalidade consideráveis. Mais de 500 mil mulheres desenvolvem carcinoma de colo uterino a cada ano no mundo, sendo que 85% dos casos ocorrem nos países em desenvolvimento (FERLEY, 2008). No ano de 2012, a estimativa do Instituto Nacional do Câncer (INCA) no Brasil é de 17.540 novos casos de câncer do colo uterino, aproximadamente 17 casos para cada 100 mil mulheres. Cerca de 850 casos novos são esperados no Rio Grande do Sul (INCA, 2012). A histerectomia radical com linfadenectomia é uma das opções recomendadas para o tratamento do carcinoma de colo uterino inicial (WIEBE, 2012), realizada preferencialmente pela via abdominal (RAMIREZ, 2008a).

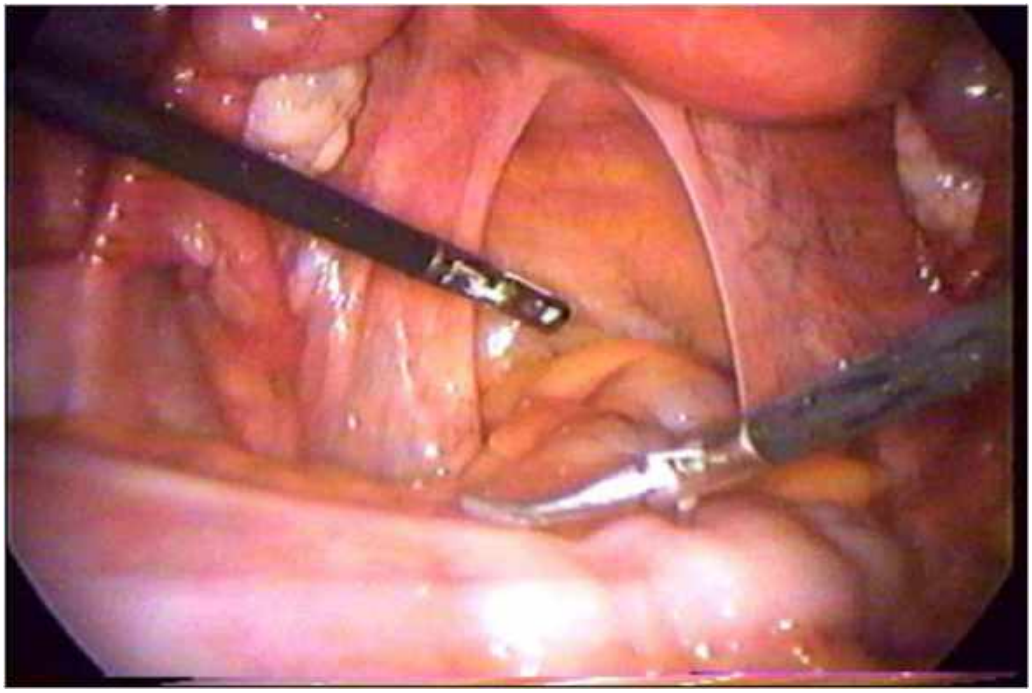
As taxas de cura do carcinoma de colo uterino nos estádios IB e IIA tratados pela histerectomia radical com linfadenectomia são superiores a 80% para os tumores menores de 4 centímetros (cm) e em torno de 70% para as pacientes com tamanho tumoral superior a 4 cm (LANDONI, 1997; DELGADO, 1990). Tamanho tumoral maior que 4 cm, invasão do espaço linfovascular e linfonodos positivos diminuem a sobrevida livre de doença, indicando a necessidade de tratamento adjuvante (LANDONI, 1997; WIEBE, 2012). Radioterapia e cirurgia, quando comparadas em ensaios clínicos randomizados, mostraram taxas similares de sobrevida (LANDONI, 1997; NEWTON, 1975).

Os benefícios da abordagem laparoscópica, comparada à abordagem abdominal, para o tratamento de patologias ginecológicas benignas incluem diminuição da dor pós-operatória e menor tempo de internação (MEDEIROS, 2008; KLUIVERS, 2007). Alguns estudos randomizados descreveram um tempo cirúrgico aumentado (KLUIVERS, 2007; HOLZER, 2006).

Estudos prévios já descreveram a factibilidade e a segurança da histerectomia radical laparoscópica (HRL) (SPIRTOS, 2002; RAMIREZ, 2006; OBERMAIR, 2003). A histerectomia radical laparoscópica (Figura 1) em estudos comparativos não randomizados apresentou maior tempo cirúrgico (FRUMOVITZ, 2007; ZACHASHANSKY, 2007; LI, 2007), menor tempo de internação (FRUMOVITZ, 2007; ZACHASHANSKY, 2007) e menor taxa de infecção pós-operatória (FRUMOVITZ, 2007) quando comparada à histerectomia radical abdominal (HRA). Um estudo comparando variáveis histopatológicas da HRL e da HRA sugeriu que

elas têm a mesma radicalidade (GHEZZI, 2007). Dados preliminares sugerem uma sobrevida equivalente nas duas técnicas (LI, 2007; DIAZ-FEIJOO, 2008). Estudo recente não controlado com 12 anos de seguimento de 240 pacientes que realizaram histerectomia radical laparoscópica descreveu taxas de sobrevida livre de doença para os estádios IA2, IB1, IB2 e IIA de 100%, 82%, 66% e 60%, respectivamente (YAN, 2011). Estudo de caso-controle retrospectivo publicado em 2012 comparou 24 casos e 48 controles nos estádios IA2-IIA pareados por cirurgião, idade, estádio e histologia. O tempo médio de internação foi significativamente menor no grupo da HRL, comparado com a HRA (10,7 dias e 18,8 dias, respectivamente; $p < 0,01$). Não houve diferença estatisticamente significativa na sobrevida livre de doença em cinco anos entre os grupos (90,5% e 93,3%, respectivamente; $p = 0,918$), com um tempo médio de seguimento de 78 meses para a HRL e 75 meses para a HRA. A taxa de recidiva foi de 8,3%, tanto para as pacientes que realizaram HRL quanto para as pacientes que realizaram a HRA. (LEE, 2011).

Figura 1 – Histerectomia radical laparoscópica realizada pela equipe cirúrgica do estudo



Fonte: a autora (2013)

1.1 ETIOLOGIA E FATORES DE RISCO

O principal agente etiológico implicado no desenvolvimento do carcinoma de colo uterino e das suas lesões precursoras é o papilomavírus humano (HPV), sendo que mais de 95% dos carcinomas cervicais contêm o DNA (ácido desoxirribonucleico) do vírus HPV (BOSH, 2003; WAGGONER, 2003; SHIFFMAN, 2011). O vírus é adquirido principalmente pela via sexual (WAGGONER, 2003; INTERNATIONAL COLLABORATION OF EPIDEMIOLOGICAL STUDIES OF CERVICAL CANCER, 2009). Os subtipos virais mais claramente implicados com as neoplasias anogenitais são 16, 18, 31, 33, 35, 39, 45, 51, 52 e 58, sendo que os subtipos 16 e 18 são os mais frequentes (BOSH, 2003; WAGGONER, 2003; INSINGA, 2008). As proteínas E6 e E7 são as oncoproteínas primárias do HPV, tendo como alvos mais importantes a supressão da proteína 53 (p53) e da proteína do retinoblastoma (pRB). A inibição da p53 por E6 bloqueia a aptose, enquanto a inibição da pRB interrompe a parada do ciclo celular (SCHIFFMAN, 2007). A infecção pelo HPV pode não ser suficiente para o estabelecimento do processo neoplásico, havendo possivelmente outros fatores atuando em conjunto com o HPV (INTERNATIONAL COLLABORATION OF EPIDEMIOLOGICAL STUDIES OF CERVICAL CANCER, 2009; CASTELSAGUÉ, 2003; WANG, 2009).

Os cofatores podem atuar na carcinogênese de três maneiras, influenciando o contágio do vírus, aumentando o risco de persistência ou facilitando a carcinogênese propriamente dita (CASTELSAGUÉ, 2003). O tabagismo, por exemplo, é um fator de risco independente associado ao carcinoma invasor (WANG, 2009; KAPEU, 2009). Mulheres positivas para subtipos oncogênicos de HPV que fumam têm 2,5 mais chances de ter o diagnóstico de neoplasia intraepitelial cervical de grau 3 (NIC3), com um intervalo de confiança de 95% (IC 95%) de 1,8-3.3,6 do que não fumantes (WANG, 2009). Metanálise recente confirmou a associação entre tabagismo e carcinoma de colo uterino com uma *odds ratio* (OR, razão de chance) de 1,73, IC 95%: 1,35-2,21 (ZENG, 2012).

Associação entre carcinoma de colo uterino e paridade aumenta com o aumento da prole (OR: 3,88; IC 95%: 1,99 a 7,55; para cinco ou mais filhos) (CASTELSAGUÉ, 2003). O aumento do risco associado ao uso dos contraceptivos orais é controverso (CASTELSAGUÉ, 2003; WANG, 2009). Estudo delineado para avaliar comportamento sexual e o risco de HPV que agrupou dados de outros

estudos epidemiológicos detectou uma associação entre carcinoma de colo uterino e início precoce da atividade sexual, antes dos 14 anos (OR: 2,05; IC 95%: 1,54-2,73), e carcinoma de colo e número de parceiros sexuais superior a seis (OR: 2,78; IC 95%: 1,83-2,92) (INTERNATIONAL COLLABORATION OF EPIDEMIOLOGICAL STUDIES OF CERVICAL CANCER, 2009). Pacientes recebendo agentes imunossupressores (WAGGONER, 2003) e portadoras do vírus da imunodeficiência humana (HIV) (FRISH, 2000) também têm um risco aumentado de desenvolver carcinoma de colo uterino. Coorte publicada recentemente descreveu um risco estatisticamente significativo para carcinoma de colo uterino em pacientes com síndrome metabólica, com um *hazard ratio* (HR, razão de danos) de 1,26; IC 95%: 1,09-1,47 (ULMER, 2012).

1.2 DIAGNÓSTICO E HISTOPATOLOGIA

O diagnóstico de carcinoma de colo uterino deve ser feito mediante confirmação histopatológica de lesão suspeita, seja por biópsia ou conização do colo uterino (WAGGONER, 2003). O diagnóstico nos estádios IA1 e IA2 deve ser preferencialmente realizado por conização do colo uterino (WIEBE, 2012; WAGGONER, 2003). Os dois subtipos histológicos mais comuns do carcinoma de colo uterino são carcinoma escamoso e adenocarcinoma. Os carcinomas escamosos do colo se originam da junção escamocolunar e correspondem a cerca de 70% dos carcinomas de colo. Os adenocarcinomas compreendem 25% dos tumores e se originam das células glandulares da endocérvix. Existe controvérsia na literatura sobre o possível pior prognóstico do adenocarcinoma (LEA, 2012; MABUCHI, 2012) No Quadro 1, podem ser visualizados os tipos histológicos de carcinoma de colo uterino.

Quadro 1 – Tipos histológicos de carcinoma de colo uterino

Carcinoma escamoso	
Adenocarcinoma	Adenocarcinoma endocervical Adenocarcinoma endometrioide Adenocarcinoma de desvio mínimo Adenocarcinoma papilar viloglandular Adenocarcinoma seroso Adenocarcinoma de células claras Adenocarcinoma mesonéfrico
Carcinomas cervicais mistos	Carcinoma adenoescamoso Carcinoma *glassy cell* Carcinoma adenoide cístico Epitelioma basal adenoide
Tumores neuroendócrinos	Tumor neuroendócrino de grandes células Carcinoma de pequenas células
Outros tumores malignos	Sarcomas de colo uterino Linfomas Tumores metastáticos

Fonte: Lea (2012)

1.3 ESTADIAMENTO

O estadiamento do carcinoma de colo uterino deve ser estabelecido na ocasião do diagnóstico, baseado na avaliação clínica do tamanho do tumor e sua extensão para a pele, e não deve ser mudado, mesmo quando achados transoperatórios documentem doença mais avançada (WIEBE, 2012). Modificações no estadiamento da Federação International de Ginecologia e Obstetrícia (FIGO) foram feitas em 1995 para modificar a definição de carcinoma microinvasor e subdividir os carcinomas do estádio IB em IB1 e IB2 (CREASMAN, 1995). Em 2009, foi feita uma nova modificação para definir prognóstico de maneira mais acurada. A última modificação no estadiamento da FIGO é de 2009 e consta no Quadro 2 (PECORELLI, 2009).

Quadro 2 – Estadiamento da FIGO para o carcinoma de colo uterino*

Estádio	Descrição
Estádio I	Carcinoma invasor confinado ao colo uterino (extensão para o corpo uterino não deve ser considerada)
IA	Carcinoma invasor diagnosticado somente pela microscopia, com profundidade de invasão máxima de 5 mm e extensão horizontal máxima de 7 mm
IA1	Invasão do estroma ≤ 3 mm de profundidade, ≤ 7 mm de extensão horizontal
IA2	Invasão do estroma entre > 3 e ≤ 5 mm de profundidade, ≤ 7 mm de extensão horizontal
IB	Lesões clinicamente visíveis restritas ao colo ou lesões pré-clínicas maiores do que IA
IB1	Lesões clínicas ≤ 4 cm na sua maior dimensão
IB2	Lesões clínicas > 4 cm na sua maior dimensão
Estádio II	Tumor invade além do útero, mas não até a parede pélvica ou terço inferior da vagina
IIA	Sem invasão parametrial
IIA1	Lesões clinicamente visíveis ≤ 4 cm na sua maior dimensão
IIA2	Lesões clinicamente visíveis > 4 cm na sua maior dimensão
IIB	Invasão parametrial
Estádio III	Tumor se estende até a parede pélvica e/ou envolve o terço inferior da vagina e/ou causa hidronefrose ou rim não funcionante
IIIA	Invasão do terço inferior da vagina, sem invasão da parede pélvica
IIIB	Extensão para a parede pélvica e/ou hidronefrose ou rim não funcionante
Estádio IV	Invasão da mucosa vesical ou retal documentada histologicamente ou além da pelve verdadeira (edema bolhoso não categoriza estádio IV)
IVA	Invasão dos órgãos adjacentes
IVB	Metástase a distância

Legenda: * O envolvimento vascular/linfático não faz parte do estadiamento.
Fonte: Wiebe (2012)

A drenagem linfática do colo uterino segue rotas pré-ureterais, pós-ureterais e uterossacrais, seguindo esta ordem: linfonodos parametriais, obturadores e hipogástricos (ilíacos internos), ilíacos externos, pré-sacrais e ilíacos comuns. Linfonodos para-aórticos são a segunda estação de disseminação. Os locais mais comuns de metástases a distância incluem linfonodos aórticos e mediastinais, pulmões e ossos (WIEBE, 2012).

De acordo com as diretrizes da FIGO, os seguintes exames ou procedimentos são permitidos: exame físico, colposcopia, curetagem endocervical, histeroscopia, conização, cistoscopia, retossigmoidoscopia, urografia excretora e raios-X. Tomografia computadorizada (TC), ressonância nuclear magnética (RNM), tomografia por emissão de pósitrons (PET-TC) são permitidos, mas não obrigatórios (WIEBE, 2012). A recomendação do Ministério da Saúde do Brasil para a solicitação de exames subsidiários adicionais inclui: exames de bioquímica, raios-X de tórax e ultrassonografia abdominal e pélvica. TC, RNM e urografia excretora devem ser solicitados apenas em casos selecionados. Nos estádios III e IV, há a recomendação para a solicitação de uretrocistoscopia e retossigmoidoscopia (INCA, 2000).

Coorte delineada para avaliar a acurácia da tomografia por emissão de pósitrons com [18F] flurodeoxiglicose (FDG-PET) para o estadiamento do carcinoma de colo uterino incluiu 560 pacientes em todos os estádios. Considerando todos os estádios, 47% dos pacientes apresentaram comprometimento linfonodal pelo FDG-PET, que estratificou os pacientes em grupos com prognóstico distinto em cada estádio, sendo que o grupo com linfonodos positivos apresentou prognóstico pior ($p < 0,001$). A HR para a recorrência da doença aumentou com a distância da doença linfonodal detectada: linfonodos pélvicos, 2,40 (IC 95%: 1,63 a 3,52); para-aórticos, 5,88 (IC 95%: 3,80 a 9,09); e supraclaviculares, 30,27 (IC 95%: 16,56 a 55,34) (KIDD, 2010).

Modelo analítico de decisão foi planejado para predizer capacidade da RNM e da PET-TC em melhorar os desfechos de uma coorte de portadoras de carcinoma de colo uterino IB que realizaram RNM, PET/TC e RNM e PET/TC ou nenhum exame de imagem (apenas realização de cirurgia). A decisão para terapia correta foi mais alta com PET/TC (89,27%) e mais baixa com RNM (68,21%). A evitação da terapia trimodal foi mais alta com RNM e PET/TC (95,01%) e mais baixa no grupo sem exame de imagem (82,32%) (PANDHARIPANDE, 2009). A diretriz clínica de 2010 da FIGO para o tratamento do carcinoma de colo uterino considera a PET-TC mais acurada para predizer o comprometimento de linfonodos para-aórticos, acima de 10 mm, em comparação TC e MRI, e classifica o nível de evidência como B (WIEBE, 2012).

O estadiamento clínico é recomendado pela FIGO, pois permite a comparação entre os resultados dos diferentes tipos de tratamento em diferentes centros e países (WIEBE, 2012) e é um indicador prognóstico confiável para o

carcinoma de colo uterino. A sobrevida em cinco anos chega a 100% em pacientes no estádio IA e 70-85% no estádio IB1 e lesões pequenas do estádio IIA. A sobrevida para tumores mais localmente avançados varia e é modificada significativamente pelo volume de doença, idade e comorbidades. A sobrevida livre de doença é de 50-70% nos estádios IB2 e IIB, 30-50% no estádio III e 5-15% no estádio IV (WAGGONER, 2003).

1.4 TRATAMENTO

O tratamento do carcinoma do colo uterino para pacientes com prole definida proposto pela FIGO em 2012 está descrito no Quadro 3. A pesquisa de linfonodo sentinela ainda é considerada controversa (WIEBE, 2012).

Quadro 3 – Tratamento do carcinoma de colo uterino proposto pela FIGO

Estádio	Descrição
Estádio IA1	Histerectomia vaginal, abdominal ou laparoscópica
Estádio IA2	Histerectomia radical modificada com linfadenectomia pélvica
Estádio IB1	Histerectomia radical abdominal com linfadenectomia pélvica ou radioterapia[1]/ Quimiorradioterapia[2]
Estádio IB2	Quimiorradioterapia[2]/ Histerectomia radical abdominal com linfadenectomia pélvica[3]
Estádio IIA1	Histerectomia radical abdominal com linfadenectomia pélvica ou radioterapia[1]/ Quimiorradioterapia[2]
Estádio IIA2	Quimiorradioterapia[2]/ Histerectomia radical abdominal com linfadenectomia pélvica
Estádio IIB	Quimiorradioterapia[2]
Estádio IIIA	Quimiorradioterapia[2]
Estádio IIIB	Quimiorradioterapia[2]
Estádio IVA	Quimiorradioterapia[2] ou exenteração pélvica[4]
Estádio IVB	Tratamento paliativo

Observações: 1. Inclui radioterapia externa e braquiterapia; 2. Inclui radioterapia externa e braquiterapia com doses semanais concomitantes de cisplatina; 3. Inclui radioterapia se necessário; 4. Se invasão da bexiga e paramétrios livres.
Fonte: Wiebe (2012)

1.5 PROGNÓSTICO

Metástases em linfonodos pélvicos e linfonodos para-aórticos estão associadas à piora da sobrevida (TANAKA, 1984; DELGADO, 1990; BAALBERGER, 2004; WIEBER, 2012), e a taxa de sobrevida em cinco anos diminui quanto maior for o número de linfonodos comprometidos: 62% para um linfonodo positivo, 36% para dois linfonodos positivos, 20% para três ou quatro linfonodos positivos e zero para cinco ou mais (TANAKA, 1984). Na análise multivariada em estudo norueguês que incluiu exclusivamente 305 adenocarcinomas apenas estádio, grau de diferenciação e metástases linfonodais foram fatores prognósticos importantes para a sobrevida (BAALBERGER, 2004). Embora sejam menos de 5% dos carcinomas cervicais, os carcinomas adenoescamosos têm um prognóstico pior (WAGGONER, 2003; DOS REIS, 2007).

Em 1994, a FIGO dividiu o estádio IB em tumores menores e maiores de 4 cm (estádios IB1 e IB2) (CREASMAN, 1995) para refletir a maior taxa de recorrência e o risco de disseminação nodal dos tumores maiores (WAGGONER 2003). Em 2009, a FIGO dividiu o estádio IIA em IIA1 e IIA2, separando os tumores menores e maiores de 4 cm (PECORELLI 2009) com o mesmo objetivo. Há consenso na literatura que tamanho tumoral é um dos principais fatores prognósticos (WAGGONER, 2003; WIEBE, 2012; CHUNG, 1980; DELGADO, 1990; LANDONI, 1997; PARK, 2011).

Estudo publicado em 2011 que incluiu 1.415 portadoras de carcinoma de colo uterino dividiu as pacientes a partir do tamanho tumoral (tumores ≤ 2 cm, entre 2 e 4 cm, de 4 a 6 cm e ≥ 6 cm). A terapia adjuvante foi necessária em 13%, 34%, 56,7% e 92,9% das pacientes, respectivamente ($p < 0,01$). Os riscos de recorrência e óbito aumentavam significativamente com tamanho tumoral ajustado para outros fatores na análise multivariada ($p < 0,001$ para os dois desfechos). Mesmo para pacientes sem fatores de risco intermediários ou altos, o tamanho tumoral foi um preditor de menor tempo de sobrevida e sobrevida livre de doença ($p < 0,001$ para os dois desfechos) (PARK, 2011).

A invasão do espaço linfático ou vascular (IELV) é um fator prognóstico independente para a recorrência (DELGADO, 1990; KAMELLE, 2004; RUTLEDGE, 2004; MARCHIOLÉ, 2005). Estudos prospectivos avaliando características histopatológicas de 732 pacientes com carcinoma escamoso de colo uterino no estádio I tratadas com cirurgia radical verificou que, além das metástases

linfonodais, o tamanho do tumor, a invasão estromal profunda e a invasão do espaço linfovascular (IELV) foram fatores prognósticos independentes para a recorrência. A sobrevida livre de recorrência para pacientes com linfonodos pélvicos negativos e portadoras das três variáveis histopatológicas foi de 60% em três anos (DELGADO, 1990). Estudo de caso-controle incluiu 26 casos de pacientes submetidas à histerectomia radical vaginal que recidivaram em 36 meses, e também 26 controles submetidos à mesma cirurgia, pareadas por idade, tipo histológico, estádio cirúrgico e tamanho tumoral. O risco relativo (RR) para a recorrência foi de 2,64 (IC 95%: 1,67-5,49) para as pacientes que apresentaram IELV (MARCHIOLÉ, 2005).

Outro estudo publicado em 2004 comparou 109 pacientes no estádio IB1 e 86 pacientes no estádio IB2 e concluiu que apenas a invasão do espaço linfovascular (OR: 6,4; IC 95%: 2,4-17) e o envolvimento parametrial (OR: 8; IC 95%: 3,1-20) são preditores independentes da positividade linfonodal. Tanto o tamanho tumoral quanto a positividade linfonodal foram associados à sobrevida livre de doença. Esses autores sugeriram que o tamanho tumoral não é o preditor primário do prognóstico, mas um marcador que influencia o desfecho através da presença de outros fatores de alto risco (RUTLEDGE, 2004).

Em revisão ampla da literatura publicada em 1996, na medida em que aumenta a profundidade da invasão estromal, aumenta a incidência de envolvimento do espaço linfovascular. Nas lesões com invasão menor de 1 milímetro (mm), 4,4% das pacientes apresentam envolvimento do espaço linfovascular em comparação a 19,7% quando a invasão está entre 3-5 mm de profundidade. Quinze por cento das pacientes no estádio IA2 com invasão do espaço linfovascular apresentaram recidiva tumoral, e apenas 1,7% das pacientes sem envolvimento do espaço linfovascular tiveram o mesmo desfecho (BENEDET, 1996).

Estudo retrospectivo delineado para associar características histopatológicas da biópsia pré-operatória (conização a frio ou por cirurgia de alta frequência) e o comprometimento linfonodal na histerectomia radical incluiu 88 pacientes. IELV e profundidade de invasão maior de 4 mm foram estatisticamente associadas com comprometimento linfonodal (25,6% *versus* 4,8%, p = 0,01, e 25% *versus* 4,5%, p = 0,01, respectivamente). O risco de comprometimento linfonodal foi seis vezes maior (IC 95%: 2,1-21,9) se a paciente apresentasse IELV e invasão maior de 4 mm associadas (MILAM, 2007).

Na presença de invasão linfovascular no estádio IA2 existe a recomendação para histerectomia radical (Piver II) com linfadenectomia (WAGGONER, 2003; WIEBE, 2012; NCCN, 2012) ou radioterapia (WAGGONER, 2003; NCCN, 2012) para as pacientes com prole definida. Para as pacientes sem prole ou com prole incompleta existe a possibilidade de realização de conização (se margens livres) ou traquelectomia radical e linfadenectomia laparoscópica (NCCN, 2012; WIEBE, 2012).

O tratamento no estádio IB deve levar em conta o tamanho do tumor, a idade da paciente, a presença de comorbidades e os recursos disponíveis no local de tratamento. Após a subdivisão do estádio IB em 1994, estudo incluiu pacientes nos estádios IB1 e IB2 tratadas com histerectomia radical e linfadenectomia. O único fator predisponente para complicações pós-operatórias detectado em regressão logística foi a realização de linfadenectomia para-aórtica (RR: 2,38; IC 95%: 1,36-4,15). As pacientes no estádio IB2 tiveram uma menor sobrevida em cinco anos (72,8%) em comparação às pacientes no estádio IB1 (90%; p = 0,0265). Na análise multivariada, diâmetro tumoral, positividade dos linfonodos e índice de massa corporal tiveram impacto na sobrevida. Não foi detectado um impacto independente do estádio tumoral na sobrevida e os autores concluíram que o estádio influencia a sobrevida pela maior possibilidade de comprometimento linfonodal (FINAN, 1996).

A controvérsia em relação ao melhor tratamento para o carcinoma de colo uterino inicial existe há muitas décadas (FINAN, 1996; ACKERMANN, 2004; RUTLEDGE, 2004; WIEBE, 2012), e tanto a radioterapia quanto a cirurgia radical podem ser efetivas (NEWTON, 1975; PIVER, 1988; LANDONI, 1997). Ensaio clínico randomizado publicado em 1975, incluindo pacientes no estádio I do carcinoma de colo uterino, comparou 61 pacientes tratadas com radioterapia com 58 pacientes tratadas com histerectomia radical. A sobrevida em 10 anos foi de 75% para pacientes tratadas com cirurgia e 65% para tratadas com radioterapia, sem diferença estatisticamente significativa (NEWTON, 1975). Em estudo publicado em 1988, 55 pacientes submetidas à histerectomia radical com linfadenectomia e 48 pacientes submetidas à radioterapia e à braquiterapia foram comparadas. Incluíram-se apenas pacientes com tumores menores de 3 cm. A sobrevida livre de doença em cinco anos foi de 92,3% para pacientes tratadas cirurgicamente e 91,1% para as pacientes tratadas com radioterapia (PIVER, 1988).

Ensaio clínico randomizado comparando tratamento cirúrgico com radioterapia incluiu 343 mulheres nos estádios IB e IIA que foram randomizadas para

receber cirurgia radical e linfadenectomia pélvica (172) ou radioterapia (171). As pacientes foram estratificadas pelo tamanho tumoral (menor ou igual a 4 cm e maior de 4 cm). Pacientes com envolvimento estromal profundo, comprometimento parametrial, margens exíguas e linfonodos positivos receberam radioterapia adjuvante. A terapia adjuvante foi realizada em 54% das pacientes com tumores menores de 4 cm e 84% das pacientes com tumores maiores de 4 cm. Estas últimas apresentaram uma maior frequência de comprometimento parametrial e IELV. A sobrevida global para pacientes submetidas à cirurgia e para pacientes submetidas à radioterapia, estratificada por tamanho tumoral, não diferiu estatisticamente entre os grupos (para tumores menores de 4 cm, 87% e 90%; para tumores maiores de 4 cm, 70% e 72%, respectivamente). A sobrevida livre de doença para pacientes submetidas à cirurgia e para pacientes submetidas à radioterapia também não diferiu estatisticamente entre os grupos (para tumores menores de 4 cm, 80% e 82%; e para tumores maiores de 4 cm, 63% e 57%, respectivamente). Quarenta e oito pacientes (28%) no grupo cirurgia apresentaram morbidade severa comparadas com 19 (12%) no grupo radioterapia (p = 0,0004) (LANDONI, 1997).

Metanálise publicada em 2008 foi delineada com o objetivo de avaliar o efeito da adição da quimioterapia simultânea à radioterapia comparada com radioterapia para o tratamento carcinoma de colo uterino inicial. Foram incluídas 3.452 pacientes. Houve uma melhora de 8% na sobrevida livre de doença em cinco anos com a quimiorradioterapia (HR: 0,78; IC 95%: 0,70-0,87), tanto para pacientes que usaram derivados da platina ou não derivados. Os benefícios foram mais claramente observados nos estádios IB-IIA. Efeitos adversos agudos hematológicos e gastrointestinais foram mais comuns no grupo que realizou quimiorradioterapia (CHEMORRADIOTHERAPY GROUP, 2008). A quimiorradioterapia tem nível de evidência A na última diretriz da FIGO. O tratamento mais comumente utilizado é radiação externa e braquiterapia intracavitária adicionadas à quimioterapia a base de platina semanal. As doses de radiação sugeridas seriam entre 45 a 50 Gy e 180-200 cGy. Nas pacientes com linfonodos pélvicos e para-aórticos positivos, a radioterapia com campos estendidos deveria ser considerada (nível de evidência C na última diretriz clínica da FIGO) (WIEBE, 2012).

1.6 HISTERECTOMIA RADICAL E RADIOTERAPIA

Existem algumas vantagens do tratamento cirúrgico em relação à radioterapia, especialmente em mulheres mais jovens e se este for o único tratamento necessário. O tempo de tratamento é mais curto, a função ovariana é preservada, a extensão acurada da doença é estabelecida e as sequelas tardias de radiação são evitadas (WAGGONER, 2003; ACKERMANN, 2004; BANSAL, 2009). Entretanto, se tratamento adjuvante com radioterapia for necessário, essa vantagem desaparece (MOORE, 2006; ACKERMANN, 2004; BANSAL, 2009). Mesmo se a transposição ovariana for realizada, a preservação da função ovariana ocorre em apenas 50% das pacientes (FEENEY, 1995).

Estudo avaliou pacientes submetidas à histerectomia radical (37) ou radioterapia (37) cinco anos após o tratamento, e essas pacientes foram comparadas a um grupo controle (40), pareado por idade e raça, sem diagnóstico de neoplasia. As pacientes tratadas com radioterapia apresentaram piores escores de qualidade de vida, estresse psicossocial e função sexual do que as pacientes que fizeram cirurgia e do que o grupo controle – esses dois últimos com escores similares (FRUMOVITZ, 2005). Outro estudo comparando a qualidade de vida e as complicações de longo prazo da histerectomia radical e da radioterapia incluiu 202 pacientes. Constipação ($p < 0,001$), disúria ($p < 0,001$), incontinência urinária ($p < 0,01$), dispareunia ($p < 0,05$) e ressecamento vaginal ($p < 0,05$) foram estatisticamente mais frequentes no grupo que realizou cirurgia. Diarreia ($p < 0,01$), hematoquezia ($p < 0,001$) e dor abdominal foram mais ($p < 0,01$) frequentes no grupo radioterapia. Não houve diferença na frequência de disfunção sexual entre os grupos (HSU, 2009).

As indicações clássicas de radioterapia após a histerectomia radical incluem: margens comprometidas ou exíguas, extensão aos paramétrios e metástases linfonodais. A radioterapia pós-operatória está associada a menores taxas de recorrência em comparação a nenhum tratamento para pacientes no estádio IB com características histopatológicas desfavoráveis (MOORE, 2006; SEDLIS, 1999). Estudo incluiu 277 pacientes no estádio IB submetidas à histerectomia radical com linfadenectomia com linfonodos negativos, portadoras de outras variáveis de mau prognóstico: mais de 1/3 de invasão estromal, invasão dos espaços capilares linfáticos e tamanho tumoral. As pacientes foram randomizadas para receber

radioterapia pélvica adjuvante (137) ou nenhum tratamento (140). Vinte e uma pacientes (15%) que fizeram radioterapia e 39 pacientes (28%) no grupo que não recebeu tratamento posterior apresentaram recidiva da doença. No grupo radioterapia, 13% das pacientes foram a óbito devido ao carcinoma e 21% no grupo sem tratamento posterior. Houve uma redução de 47% no risco de recidiva com a radioterapia adjuvante (p = 0,008), com um aumento nos efeitos adversos graves (SEDLIS, 1999). Ensaio clínico randomizado de 1997, comparando a histerectomia radical com linfadenectomia e radioterapia nos estádios IB e IIA, descreveu taxas de cura que foram similares entre cirurgia e radioterapia, mas 54% das pacientes com tumores menores de 4 cm e 84% das pacientes com tumores maiores de 4 cm no grupo submetido à cirurgia necessitaram de radioterapia adjuvante (LANDONI, 1997). Estudo de custo-efetividade descreveu a histerectomia radical com linfadenectomia pélvica e para-aórtica como sendo a estratégia terapêutica mais custo-efetiva em contextos onde recursos financeiros são limitados (ROCCONI, 2005).

Uma área de particular controvérsia no tratamento cirúrgico radical dos carcinomas de colo uterino IB2 seria morbidade associada da histerectomia radical e radioterapia pélvica combinadas. A despeito da vantagem na sobrevida detectada com o uso de radioterapia adjuvante (SEDLIS, 1999) e da quimiorradioterapia adjuvante concomitante para tumores volumosos de mau prognóstico (PETERS, 2000), alguns estudos relataram um aumento na morbidade com o uso dos dois tratamentos (SEDLIS, 1999; PETERS, 2000; KJORSTAD, 1983), enquanto outros não detectaram diferença nas taxas de complicações (LANDONI, 1997; HAVRILESKY, 2004).

1.7 HISTERECTOMIA RADICAL

A histerectomia radical foi descrita pela primeira vez em 1895 por Clark, e em 1912 Wertheim publicou uma série de 500 pacientes, sendo que a linfadenectomia não era rotineiramente realizada. A mortalidade do procedimento era alta naquela época, em torno de 19%. Em função disso, o tratamento preconizado era a radioterapia. Em 1951, Meigs publicou uma série de 100 pacientes submetidas à histerectomia radical e incorporou a linfadenectomia pélvica ao procedimento. Todas as pacientes sobreviveram à cirurgia. A classificação mais utilizada das variantes da

histerectomia radical foi proposta por Piver e Rutledge (1974), que pode ser visualizada no Quadro 4.

Quadro 4 – Classificação de Piver-Rutledge para a histerectomia no tratamento do carcinoma cervical

1	Histerectomia extrafascial.
2	Histerectomia radical modificada. Remoção de 50% dos paramétrios e ligamentos uterossacros. Os vasos uterinos são ligados medialmente aos ureteres.
3	Equivalente à cirurgia de Wertheim-Meigs. Ampla dissecção dos tecidos parametriais e paravaginais com ligadura da artéria uterina na sua emergência da artéria ilíaca interna. O ureter é dissecado completamente até a sua entrada da bexiga. O ligamento uterossacro é ligado na sua origem. Ligamentos cardinais ligados na parede pélvica. Remoção da metade da vagina. A linfadenectomia pélvica é geralmente realizada.
4	O ureter é separado do ligamento pubovesical. A artéria vesical superior é ligada e os dois terços superiores da vagina excisados.
5	Histerectomia radical estendida para bexiga ou ureter distal.

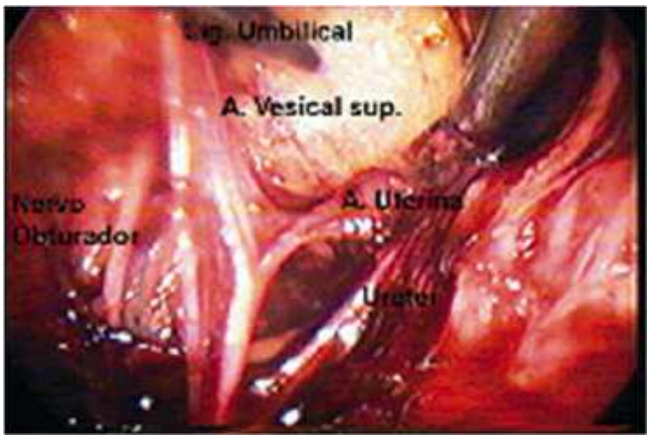
Fonte: Piver e Rutledge (1974)

O objetivo da histerectomia radical é retirar o tumor inicial com margens adequadas de tecido normal. A maioria das histerectomias radicais é de tipo 2 ou 3 ou variante das duas, o que dificulta as comparações entre as técnicas. A linfadenectomia pélvica é parte do tratamento cirúrgico de carcinoma de colo uterino 1B-2A (HOLLAND, 2005). A média de linfonodos removidos é de 23 (TRIMBOS, 2004). O número de linfonodos pélvicos excisados é considerado um dos critérios de qualidade para a histerectomia radical. A remoção dos paramétrios, da porção superior da vagina e exérese de linfonodos pélvicos são consideradas as etapas de maior impacto no desfecho (VERLEYE, 2009).

A extensão e a qualidade da cirurgia influenciam no número de complicações perioperatórias, pertinência da terapia adjuvante, sobrevida global, controle local do tumor e provavelmente na sobrevida. Todos os esforços precisam ser envidados para oferecer às pacientes uma cirurgia de alta qualidade para assegurar os parâmetros ideais de desfecho. Indicação, radicalidade e novas técnicas estão em discussão na literatura. O Grupo de Câncer Ginecológico da Organização Europeia para a Pesquisa e Tratamento do Câncer (EORTC-GCG) propõe três domínios para a qualidade da histerectomia radical para o tratamento do carcinoma ginecológico:

qualidade estrutural, qualidade de indicadores e qualidade de processo, que podem ser visualizados no Quadro 5 (VERLEYE, 2009). Na Figura 2, podem ser observados reparos.

Figura 2 – Proximidade entre a artéria uterina, ureter, artéria vesical superior e nervo obturador



Fonte: a autora (2013)

A taxa de complicações no transoperatório da histerectomia radical está entre 1% e 11% (HOLLAND, 2005; TRIMBOS, 2004; WRIGHT, 2012). As estruturas em maior risco são ureteres, bexiga, reto e estruturas vasculares (HOLLAND, 2005). O dano ureteral ocorre em 0,6% a 2,3% das histerectomias (RUTLEDGE, 2004; HOLLAND, 2005; TRIMBOS, 2004; WRIGHT, 2012). Durante a linfadenectomia as estruturas em maior risco são os vasos pélvicos, embora o seu dano seja incomum. Dano neurológico ocorre em aproximadamente 1% dos pacientes, sendo os nervos genitofemoral e o obturador os mais envolvidos (HOLLAND, 2005). A Figura 2 apresenta a proximidade entre a artéria uterina, o ureter, a artéria vesical superior e o nervo obturador.

A taxa de complicações pós-operatórias descritas varia conforme os critérios utilizados nos estudos, variando entre 11% e 16% (HAVRILESKY, 2004; RUTLEDGE, 2004; WRIGHT, 2012). As complicações pós-operatórias mais comuns são infecção urinária (TRIMBOS, 2004), disfunção vesical (HOLLAND, 2005) e infecção da ferida operatória (TRIMBOS, 2004; HAVRILESKY; 2004; HOLLAND, 2005). Eventos tromboembólicos são as complicações clínicas mais comumente descritas, oscilando entre 0,8% e 4% (NEWTON, 1975; FINAN, 1996; LANDONI, 1997; RUTLEDGE, 2004; TRIMBOS, 2004; WRIGHT, 2012).

A disfunção vesical funcional é um sintoma comum após a histerectomia radical (NEWTON, 1975; LANDONI, 1997; HOLLAND, 2005; JACKSON, 2006), sendo que até 70% das mulheres podem apresentar algum grau de disfunção. Esse fenômeno é parcialmente compreendido e parece estar relacionado à interrupção das vias simpáticas e parassimpáticas da pelve (HOLLAND, 2005; JACKSON, 2006). Por essa razão, há a necessidade de sondagem no pós-operatório, que pode ser realizada por sondagem de demora por cistostomia ou autossondagem (NAIK, 2005). O fenômeno leva entre seis e 24 meses para desaparecer (NEWTON, 1975; HOLLAND, 2005; JACKSON, 2006), sendo que 30% dessas pacientes podem apresentar algum grau de disfunção permanente (JACKSON, 2006).

As lesões ureterais ocorrem durante a dissecção parametrial, e esse risco aumenta com a radicalidade da dissecção (HOLLAND, 2005). As fístulas e estenoses ureterais são frequentemente descritas, oscilando entre 1% e 3% (LANDONI, 1997; HAVRILESKY, 2004; TRIMBOS, 2004; RUTLEDGE, 2004). Algumas fístulas ou estenoses ureterais evoluem para hidronefrose, mesmo na ausência de lesão cirúrgica detectável (PAICK, 2003). Fístulas intestinais também foram descritas (TRIMBOS, 2004; HAVRILESKY, 2004; SEDLIS, 1999). A mortalidade relacionada à histerectomia radical é estimada em cerca de 1% (TRIMBOS, 2004; WRIGHT, 2012). O Quadro 5 propõe indicadores de qualidade da histerectomia radical laparoscópica, conforme Verleye (2009).

Quadro 5 – Indicadores de qualidade para a histerectomia radical e linfadenectomia pélvica proposta pela EORTC-GCG*

	Indicador de qualidade	**Padrão definido**
Estrutura	Número de histerectomias radicais por cirurgião por ano	≥ 10
	Número de histerectomias radicais por instituição por ano	≥ 20
Desfecho	Sobrevida em cinco anos das pacientes submetidas a histerectomia radical (estádios I-IIA)	≥ 80%
	Percentual de pacientes que apresentaram recorrência da doença	≤ 15%
	Percentual de pacientes apresentando complicações de curto prazo pós-cirurgia	Mortalidade pós-operatória ≤ 1% Hemorragia pós-operatória ≤ 1% Lesão ao trato urinário ≤ 1% Obstrução intestinal ≤ 1% Trombose venosa profunda ≤ 3%
	Percentual de pacientes apresentando complicações de longo prazo pós-cirurgia	Linfocele ou sintomática ≤ 5% Estenose uretral ≤ 3% Hérnia incisional ≤ 3% Fístula com necessidade de correção cirúrgica ≤ 3%
	Percentagem de tumor com margens positivas	≤ 5%
Processo	Percentual de cirurgias com descrição integral da via de abordagem, radicalidade e tempos cirúrgicos	≥ 95%
	Percentual de linfadenectomias com mais de 11 linfonodos retirados	≥ 90%
	Percentual de linfadenectomias que contenham pelo menos um linfonodo retirado das ilíacas comuns, externas, internas e fossa obturadora	≥ 95%
	Percentual de cirurgias sem sutura do peritônio e drenagem retroperitoneal	≥ 95%
	Percentual de pacientes que receberam antibioticoterapia profilática pré-operatória	≥ 95%
	Percentual de pacientes que iniciam dieta normal no primeiro dia de pós-operatório	≥ 90%

* European Organization for Research and Treatment of Cancer – Gynecological Cancer Group
Fonte: Verleye (2009)

1.8 HISTERECTOMIA RADICAL LAPAROSCÓPICA

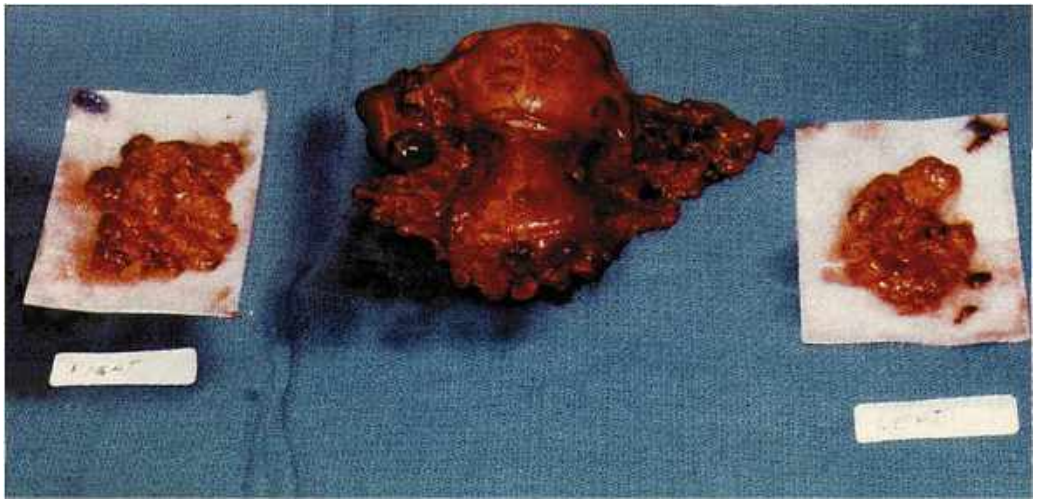
Desde o primeiro relato de linfadenectomia pélvica laparoscópica no tratamento do carcinoma de colo uterino em 1987 (DARGENT, 2005), diversas técnicas laparoscópicas para o tratamento do carcinoma do colo uterino e endométrio têm sido descritas. Redução no tempo de internação hospitalar, menor custo e redução no tempo de retorno às atividades normais foram descritos nas primeiras comparações entre a histerectomia laparoscópica (13) e a histerectomia abdominal (17) para o tratamento do carcinoma de endométrio em 1996 (SPIRTOS, 1996a). Comparação retrospectiva entre a técnica laparoscópica e a extraperitoneal para realização de linfadenectomia em um grupo de 42 portadoras de carcinoma de colo uterino submetidas à histerectomia radical vaginal detectou menor número de linfonodos retirados: 18 *versus* (*vs.*) 32. ($p < 0,05$). O mesmo estudo detectou também maior tempo cirúrgico para a técnica laparoscópica (68 min. *vs.* 48 min.; $p < 0,05$). Os grupos não diferiram em dor pós-operatória medida pela Escala Visual Analógica (LARCIPRETE, 2006). Estudo randomizou 168 pacientes que tinham indicação de histerectomia radical para realizarem linfadenectomia extraperitoneal, transperitoneal ou laparoscópica. Apesar de o número médio de linfonodos retirados nos três grupos ter sido considerado adequado, ele foi significativamente menor no grupo da laparoscopia ($36 \pm 7,2$; $35 \pm 6,9$; e $30 \pm 6,7$, respectivamente; $p < 0,01$) (PANICI, 2006).

Foram descritas histerectomia radical completamente laparoscópica com abordagem vaginal apenas para retirada da peça (SPIRTOS, 1996b) e histerectomia radical vaginal assistida por laparoscopia (SCHNEIDER, 1996). As descrições de histerectomia radical vaginal têm algumas diferenças a respeito de quais tempos cirúrgicos são realizados pela abordagem laparoscópica ou pela abordagem vaginal. Em comum, existe a dissecção de tecidos parauterinos ou paracervicais pela via vaginal após a colpotomia (SCHNEIDER, 1996; QUERLEU, 1993).

A primeira descrição de histerectomia radical inteiramente laparoscópica (HRL) foi feita por Nezhat *et al*. em 1992, que descreveram a realização do procedimento em uma paciente portadora de carcinoma de colo uterino IA2, com um tempo cirúrgico de sete horas e 14 linfonodos pélvicos e para-aórticos retirados (NEZHAT, 1992). Em 1996, foi publicada uma série com 10 pacientes submetidas à HRL, apenas com a retirada da peça pela vagina. Os autores descreveram as

medidas parametriais e vaginais da peça cirúrgica e propuseram que essa informação passasse a ser registrada nos próximos estudos, como uma medida da radicalidade da cirurgia (SPIRTOS, 1996b) (Figura 3).

Figura 3 – Peça de histerectomia radical laparoscópica realizada pela equipe do estudo



Fonte: a autora (2013)

Os estudos iniciais descreveram uma taxa aceitável de complicações (KIM, 1998; SPIRTOS, 1996b). Entretanto havia poucos dados disponíveis sobre a morbidade da histerectomia radical laparoscópica e sobrevida de longo prazo. Os resultados de alguns estudos sem grupo controle estão descritos no Quadro 6. Dados referentes às complicações cirúrgicas desses mesmos estudos não controlados estão descritos no Quadro 7. Dados de estudos comparativos estão descritos no Quadro 8. E dados referentes às complicações desses mesmos estudos controlados estão descritos no Quadro 9.

Os estudos descrevem o tempo de sutura da cúpula vaginal tanto pela via vaginal (KIM, 1998; XU, 2007; DIAZ-FEIJOO, 2008; PELLEGRINO, 2009; YAN, 2011; CHOI, 2012) quanto pela via laparoscópica (SPIRTOS, 2002; ABU-RUSTUM, 2003; OBERMAIR, 2003; GIL-MORENO, 2005; RAMIREZ, 2006; MALZONI, 2009; CANTON-ROMERO, 2010). Os artigos descrevem critérios de inclusão de pacientes bastante diferentes: desde grupos que são altamente selecionados, fazendo restrições quanto a índice de massa corporal (IMC) inferior a 30 kg/m² (POMEL, 2003; SPIRTOS, 1996), 35 kg/m² (SPIRTOS, 2002; ABU-RUSTUM, 2003; MALZONI, 2009; CANTON-ROMERO, 2010) ou 40 kg/m² (DIAZ-FEIJOO 2008); ou tamanho

tumoral inferior a 2 cm (ABU-RUSTUM, 2003), 3 cm (PELLEGRINO, 2009) e 4 cm (KIM, 1998; POMEL, 2003; CANTON-ROMERO, 2010; GIL-MORENO, 2005; PUNTAMBEKAR, 2007; RAMIREZ, 2006; ZAKASHANSKY, 2007; UCELLA, 2007; DIAZ-FEIJOO, 2008; MALZONI, 2009; CHOI, 2012); até estudos que não fazem restrição do tamanho tumoral nos estádios iniciais (SPIRTOS, 2002; OBERMAIR, 2003; GHEZZI, 2007; FRUMOVITZ, 2007; XU, 2007; LEE, 2011; YAN, 2011; NAM, 2011; PARK, 2012; HONG, 2012) ou índice de massa corporal.

1.8.1 Tempo cirúrgico

O tempo cirúrgico variou amplamente entre os estudos (Quadros 6 e 8) e a maioria dos grupos descreve tempos cirúrgicos entre 196 minutos e 363 minutos (KIM, 1998; MALZONI, 2009). Malzoni *et al.* descreveram um tempo cirúrgico de 196 minutos, incluíram 65 pacientes que realizaram HRL e abrangeram apenas pacientes com tumores menores de 4 cm e IMC inferior a 35 kg/m2. Catorze pacientes realizaram histerectomia radical modificada tipo Piver II, o que pode ter contribuído para esse tempo cirúrgico inferior a 200 minutos (MALZONI, 2009). Estudo publicado em 1998 descreveu o tempo cirúrgico mais longo, de 363 minutos (KIM, 1998). Estudo realizado em um hospital privado na Índia que incluiu 248 pacientes descreveu uma mediana de tempo cirúrgico de 92 minutos, muito inferior aos dos outros estudos (PUNTAMBEKAR, 2007), tendo sido alvo de críticas de outros autores, que consideraram pouco provável a realização de um procedimento tão extenso em um tempo cirúrgico tão diferente dos demais (RAMIREZ, 2008b).

Alguns artigos analisaram o efeito do treinamento no tempo cirúrgico, comparando os tempos cirúrgicos dos casos iniciais com os casos operados posteriormente. Pomel *et al.* compararam o tempo cirúrgico das primeiras 25 cirurgias realizadas com o tempo cirúrgico das 25 cirurgias seguintes, que foram 290 e 226 minutos, respectivamente ($p < 0,01$). Os autores atribuíram essa diminuição à curva de aprendizado da equipe cirúrgica (POMEL, 2003). Outro estudo publicado em 2007 descreveu uma diminuição no tempo cirúrgico ao longo do tempo, comparando a primeira e a segunda metade da série laparoscópica (281 ± 70 minutos e 244 ± 61 minutos, $p = 0,009$) (LI, 2007).

A maioria dos estudos com grupo comparativo do Quadro 8 descreve um maior tempo cirúrgico para a histerectomia radical laparoscópica (ABU-RUSTUM,

2003; ZAKASHANSKY, 2007; LI, 2007; DIAZ-FEIJOO, 2008; FRUMOVITZ, 2007; CHOI, 2012; MALZONI, 2009; SOLIMAN, 2011). Estudo de caso-controle recentemente publicado comparou 24 pacientes submetidas à HRL e 48 pacientes submetidas à HRA, pareadas por cirurgião, idade, estádio e histologia. Não houve diferença estatisticamente significativa entre os tempos cirúrgicos dos dois grupos (334,8 ± 52,4 *vs.* 326,8 ± 53,8) (LEE, 2011). Outro estudo de caso-controle em um programa de *fellowship*, comparando 30 pacientes que foram submetidas à HRL e 30 pacientes que foram submetidas à HRA, descreveu uma diferença estatisticamente significativa no tempo cirúrgico entre os dois grupos (318,5 minutos *vs.* 242,5 minutos, respectivamente; p = 0,01). Nesse estudo, o tempo cirúrgico da HRL realizada pelos alunos é superior a 400 minutos no início do treinamento e atinge um *plateau* em 310 minutos no terceiro ano, não diminuindo mais com o aumento da experiência do cirurgião (ZAKASHANSKY, 2007).

O estudo de caso-controle com o maior tamanho amostral publicado comparou 263 pacientes submetidas à HRL e 263 pacientes submetidas à HRA. Os controles foram pareados por metástase linfonodal, invasão parametrial, tamanho tumoral ± 2 cm, profundidade da invasão estromal (< 1/2 e > 1/2), invasão do espaço linfovascular e idade (± 3 anos). Não houve diferença estatisticamente significativa do tempo cirúrgico entre os grupos (246,8 minutos e 247,2 minutos; p = 0,982) (NAM, 2011). Nesse estudo, o grande tamanho amostral pode ter diminuído o efeito da curva de aprendizado no tempo de cirurgia laparoscópica.

Quadro 6 – Histerectomia radical laparoscópica para o tratamento do carcinoma do colo uterino inicial: estudos não controlados

Autor/ano	Nº de pacientes	FIGO*	Tempo cirúrgico (minutos)	Sangramento (ml ou cc)*	Número de linfonodos	Tempo de internação (dias)	Comentários
Spirtos (1996)	10	IA2-IB	253	300 ml	18,3	3,2	
Kim (1998)	18	IA2-IB1	363 (240-75)	619 ml (250-1000)	22 (14-40)	12	
Spirtos (2002)	78	IA2-IB	205 (150-420)	250 ml (50-700)	34,1 (19-68)	2,9 (1-7)	
Obermair (2003)	55	IA-IIA	210 (60-410)	200 ml (50-2000)	25 (2-53)	5 (2-19)	Incluiu também portadoras de outros tumores
Pomel (2003)	50	IA2-IB1 < 4 cm	258	200 cc (50-750)	13,2	7,5 (4-30)	Piver II e III
Gil-Moreno (2005)	27	IA2-IB1	285 (IC 95%: 273,31-296,5)	400 ml (250-700)	19,01 (IC 95%: 17,02-21,12)	5 (4-10)	Piver II e III
Ramirez (2006)	20	IA2-IB1	332 (275-442)	200 ml (25-700)	13 (9-26)	1 (1-5)	
Xu (2007)	317	IA2-IIB	NA	NA	NA	NA	Descreve apenas complicações
Puntambekar (2007)	248	IA2-IB1	92 (65-120)	165 ml (150-500)	18 (14-30)	3 (3-6)	
Pellegrino (2009)	107	IB1 < 3 cm	305 (220-505)	200 ml (50-550)	26 (11-48)	4 (3-9)	
Canton-Romero (2010)	54	IB1	265 (180-450)	276 ml (100-600)	19	1,5	
Yan (2011)	240	IA2, IB1, IB2 IIA, IIB	264 (100-480)	225 ml (50-2000)	23 (8-58)	13 (6-66)	
Hong (2012)	118	IA2, IB1, IB2, IIA1, IIA2	270 (120-495)	500 ml (250-1200)	26 (9-55)	7 (5-31)	Linfadenectomia para-aórtica realizada em 72% da amostra

Legenda: * estadiamento proposto pela FIGO; ** ml: mililitros; cc: centímetros cúbicos.
Fonte: a autora (2013)

Quadro 7 – Histerectomia radical laparoscópica para o tratamento do carcinoma do colo uterino: complicações e seguimento em estudos sem grupo controle

	Complicações			
Autor/ano (N)	**Transoperatórias**	**Pós-operatórias**	**Seguimento (meses)**	**Recidivas/Sobrevida**
Spirtos/1996b (10)	Nenhuma Transfusão: nenhum	Nenhuma	Sem dados de seguimento	Sem dados de seguimento
Kim/1998 (18)	Transfusão (5) 27,8%	Infecção de cúpula vaginal (2) Disfunção vesical (5) Fístula ureterovaginal (1) Estenose ureteral (1) Processos febris (2) Edema transitório de membro inferior esquerdo (1)	NI	NI
Spirtos/2002 (78)	Transfusão (1) 1,3% Taxa de complicações: 8,97% Conversão (5) 6,67% Lesão de grande vaso (2) Impossibilidade de manter pneumoperitônio (1) Lesão ureteral (1) Cistostomia (3)	Taxa de complicações: 9,1% Fístula ureterovaginal (1) TVP/EP (1) Sepse (1) Abscesso de cúpula vaginal (1) Hematoma de parede abdominal (1) Linfocele (2) Disfunção vesical transitória (2) Disfunção vesical definitiva (2)	66,8 (IC 95%: 63,29-70,28)	Sobrevida global em cinco anos: 93,6% Sobrevida livre de doença em cinco anos: 89,7% 8 recidivas 5 óbitos
Obermair/2003 (55, sendo 39 pacientes com carcinoma de colo uterino – os dados referem-se ao total de pacientes)	Transfusão (9)16,4% Taxa de complicações (4) 7,2% Conversão (3) 5,45% Lesões de grande vaso – convertidas (3) 5,45% Lesão de nervo obturador (1) 1,8%	Taxa de complicações (11) 57,9% TVP/EP (4) 1 óbito 7,2% Cistite (4) 7,2% Disfunção vesical (5) 9% Fístula vesicovaginal (1) 1,8% Fístula retovaginal (1) 1,8% Linfedema (4) 7,2% Linfocele (3) 5,45% Abscesso pélvico (2) 3,6% Hiperestesia de membro inferior (5) 9% Obstrução intestinal (1) 1,8%	36,5 (IC 95%: 18,9-54.1)	87,2% 2 óbitos por metástases 1 óbito por AVC 1 perda de seguimento

O quadro continua na página seguinte.

	Complicações			
Autor/ano (N)	**Transoperatórias**	**Pós-operatórias**	**Seguimento (meses)**	**Recidivas/Sobrevida**
Pomel/2003 (50)	Transfusão sanguínea (1) Taxa de complicações: 4% Cistostomia (1) Lesão intestinal (1)	Fístula vesical (1) Estenose ureteral (1) Disfunção vesical transitória (2) Pielonefrite (2) Evisceração por portal (1) Evisceração vaginal (1) Paralisia de plexo braquial direito (1) Dor inguinal neurogênica (1)	44	3 recidivas 1 óbito (recidiva) Sobrevida global em cinco anos: 96,8%
Gil-Moreno/2005 (27)	Conversão por falha no equipamento (1) 3,7%	Transfusão sanguínea (2) 7,41% Íleo adinânico (1) Infecção do trato urinário (2) Disfunção vesical transitória (1) Incontinência urinária de esforço (1)	32 (4-52)	100% sem evidência de doença
Ramirez/2006 (20)	Transfusão sanguínea (1) Taxa de complicações: 5% Cistostomia (1)	Evisceração (1) Pneumomediastino com enfisema subcutâneo (1) Linfocisto (1) TVP/Embolia pulmonar (1) Transfusão sanguínea (1)	8 (1-16)	Sem evidência de recidiva da doença
Xu/2007 (317)	Transfusão (4) 1,4% Taxa de complicações: 4,42% Conversões (4) 1,3% Hipercapnia (1) Lesão de cólon ascendente (1) Lesões vasculares (7) Cistostomia (5)	Fístula ureterovaginal (5) Fístula vesicovaginal (4) Estenose ureteral (1) Disfunção vesical transitória (6) Linfedema (6) Linfocele (1) TVP/EP (2) Neuropatia transitória (5)	NI	NI
Puntambekar/2007 (248)	Taxa de complicações (6%) Lesão de grande vaso (9) Cistostomia (3) Lesão ureteral (1) Lesão retal (2)	17 (6,8%) Disfunções vesicais transitórias (5) Infecções do trato urinário (2) Infecção de ferida operatória (3) Fístula ureterovaginal (4) Íleo adinâmico (2) Hemorragia (1)	36 (0-50)	6 recidivas 1 óbito

O quadro continua na página seguinte.

	Complicações			
Autor/ano (N)	**Transoperatórias**	**Pós-operatórias**	**Seguimento (meses)**	**Recidivas/Sobrevida**
Pellegrino/2009 (107)	Conversões (6) 5,61% Cistostomia (1) Lesão de nervo obturador (1)	Evisceração vaginal (2) Estenose ureteral (5) Fístula ureteral (5) Disfunção vesical transitória (22)	30	Recidiva (11) 5 óbitos recidiva 95% de sobrevida
Canton-Romero/2010 (54)	Conversão (1) 4,17% Lesão térmica intestinal com colostomia	Linfocisto (3) Disfunção vesical transitória (2) Hematoma de cúpula (1)	NI	NI
Yan/2011 (240)	Taxa de complicações: 7,08% Conversão (3) 1,25% Lesão de grande vaso (7) Cistostomia (6) Lesão ureteral (3) Lesão de nervo obturador (1)	Taxa de complicações 9,16% Fístula vesicovaginal (4) Fístula ureterovaginal (2) Linfocele (6) Linfedema (8) Obstrução intestinal (2)	35 meses (2-125)	Sobrevida IA2: 100% IB1: 82% IB2: 66% IIA: 60% 19 perdas de seguimento
Hong/2012 (118)	Transfusão: 77 (65%) Taxa de complicações: 13,5% Cistostomia (10) Lesão de grande vaso (3) Lesão ureteral (2)	Taxa de complicações: 6,7% Obstrução intestinal (1) Linfedema (2) Linfocele (3) Disfunção vesical transitória (2)	31 (1-89)	Recidivas: 8 Sobrevida: 90% Sobrevida livre de doença: 89%

Legenda: NI: não informado; TVP/EP: trombose venosa profunda/embolia pulmonar; AVC: acidente vascular cerebral
Fonte: a autora (2013)

Quadro 8 – Histerectomia radical laparoscópica e histerectomia radical abdominal para o tratamento do carcinoma do colo uterino inicial: estudos controlados

Autor/ano	Via	N	FIGO	Tempo cirúrgico (min.)	Perda sanguínea (ml ou cc)	Número de linfonodos	Tempo de permanência (dias)	Observações
Abu-Rustum (2003)	Laparoscopia	19	IA1-IB1 < 2 cm	371	301 cc	25,5	4,5	
	Laparotomia	195		295*	639 cc*	30,7	9,7*	
Li (2007)	Laparoscopia	35	IA1-IIA ≤ 5 cm	262,99	369,78 ml	21,28	13,81	
	Laparotomia	90		217,2*	455,14 ml	18,77	13,69	
Zakashansky (2007)	Laparoscopia	30	IA1-IIA ≤ 4 cm	318,5	200 cc	31	3,8	Estudo de caso-controle
	Laparotomia	30		242,5*	520 cc*	21,8*	5,6*	
Frumovitz (2007)	Laparoscopia	35	IA1-IB2	344	319 ml	13,5	2	
	Laparotomia	54		307*	548 ml*	18,7*	5*	
Ghezzi (2007)	Laparoscopia	50	IA2-IIA	285	200	21	6	Delineado para comparar variáveis histopatológicas
	Laparotomia	48		260	500*	23	10*	
Ucella (2007)	Laparoscopia	50	IA2-IIA	NI	NI	NI	NI	Delineado para avaliar complicações urinárias
	Laparotomia	48						
Diaz-Feijoo (2008)	Laparoscopia	20	IA2-IIA ≤ 4 cm	272	400 ml	18,9	4,9	Detecção de linfonodo sentinela
	Laparotomia	30		240*	623 ml*	21,6	10,7*	
Malzoni (2009)	Laparoscopia	65	IA1-IB1 < 4 cm	196	55 ml	23,5	4	
	Laparotomia	62		152*	145 ml*	25*	7*	
Lee (2011)	Laparoscopia	24	IA2-IIA	334,8	414,3 ml	26,3	10,7	Estudo de caso-controle
	Laparotomia	48		322,8	836 ml*	26,8	18,8*	
Nam (2011)	Laparoscopia	263	IA2-IIA	246,8	379,6 ml	34,3	12,5	Estudo de caso-controle
	Laparotomia	263		247,2	541,1 ml*	30,6*	20,3*	
Soliman (2011)	Laparoscopia	31	IA1-IIA	265	350	14	2	Estudo também tem um grupo em cirurgia robótica
	Laparotomia	30		338*	100*	19	4*	
Choi (2012)	Laparoscopia	105	IA1-IIA Tumores < 4 cm	268	352 ml	20,0	10,2	Estudo também tem um grupo que realizou HRVL
	Laparotomia	99		199*	480 ml*	24,4	10,7	
Park (2012)	Laparoscopia	99	IA2-IIA	253,8	433,6 ml	30,5	10,6	Pacientes com mais de 65 anos
	Laparotomia	159		271,9*	605,2 ml*	31,4	16,8*	
Wright (2012)	Laparoscopia	217	NI	NI	NI	NI	2	Amostra de 500 hospitais americanos
	Laparotomia	1.610					3*	

Legenda: min.: minutos; ml: mililitros; cc: centímetros cúbicos; cm: centímetros; NI: não informado; HRVAL: histerectomia radical vaginal assistida por laparoscopia. * P < 0,05
Fonte: a autora (2013)

Quadro 9 – Histerectomia radical laparoscópica e histerectomia radical abdominal para o tratamento do carcinoma do colo uterino inicial: estudos comparativos: complicações e seguimento em estudos controlados

		Complicações*			
Autor/ano	**Via (N)**	**Transoperatórias**	**Pós-operatórias**	**Seguimento (meses)**	**Recorrência/ sobrevida**
Abu-Rustum (2003)	Laparoscopia (19)	Conversão (2) 10,52% Sangramento (1) Cistostomia (1) Uso de stents ureterais (7) 37%	Transfusão sanguínea (1) Taxa de complicações: 5,26% Febre de origem desconhecida (1)	NI	Vivas: 100%
	Laparotomia (195)	Taxa de complicações: 5,56% Cistostomia (5) Lesão de grande vaso (5) Lesão ureteral (1)	Transfusão sanguínea (41) Taxa de complicações: 13,3% Infecção de ferida operatória (26) Infecção/hematoma pélvico (15) Obstrução intestinal (15) Íleo adinâmico (13) Infecção do trato urinário (4) Bacteremia/sepse (3) Pneumonia (1) Colite (1) TVP/PE (1) Linfedema (7)	NI	Vivas: 100%
Li (2007)	Laparoscopia (90)	Taxa de complicações (8) 8,9% Conversão (2) 2,22% (lesão de grande vaso, cistostomia) Lesão de veia ilíaca (4) Lesão vesical (4)	Taxa de complicações: 40% Disfunção vesical (29) Fístula ureteral (1) Fístula vesicovaginal (1) Obstrução intestinal (1) Linfocisto (4)	26 (5-84)	Recidiva: 13,7% Óbitos: 10% 10 perdas de seguimento
	Laparotomia (35)	Taxa de complicações(3) 8,57% Lesão de grande vaso(1) Lesão ureteral(2)	Taxa de complicações 40% Disfunção vesical(10) Obstrução intestinal(1) Linfocisto(2) Deiscência de sutura(1)	26 (5-84)	Recidiva: 12% Óbitos: 8% 5 perdas de seguimento

O quadro continua na página seguinte.

		Complicações*			
Autor/ano	**Via (N)**	**Transoperatórias**	**Pós-operatórias**	**Seguimento (meses)**	**Recorrência/ sobrevida**
Zachashansky (2007)	Laparoscopia (30)	Taxa de complicações (2) 6,67% Cistostomia e colocação de *stent* ureteral (2)	Taxa de complicações: 20% Colite (2) TVP/EP (2) Íleo adinâmico (1) Disfunção vesical (1)	20	Vivas: 100%
	Laparotomia (30)	Transfusão sanguínea (5)** Taxa de complicações (2) 6,67% Lesão de grande vaso (1) Lesão de intestino delgado com reanastomose (1)	Taxa de complicações: 26,7% Infecção de ferida operatória (1) TVP/EP (1) Íleo adinâmico (1) Obstrução intestinal (1) Disfunção vesical transitória (2) Parestesia em membro inferior (3) Pielonefrite (2)	41	Vivas: 100%
Frumovitz (2007)	Laparoscopia (35)	Transfusão sanguínea (4) 11% Taxa de complicações (4) 11,43% Conversão (2) 5,71% Lesão de grande vaso (3) Cistostomia (1)	Morbidade febril (3) CTI (3) TVP/PE (3) Neuropatia (1) Enfisema subcutâneo/ pneumodiastino (1)	7,2	Recidiva: 5,71%
	Laparotomia (54)	Transfusão sanguínea (8) 15% Cistostomia (1)	Morbidade infecciosa (10) Infecção de ferida operatória (10) CTI (8) Pneumonia (2) Abscesso intra-abdominal (2) Fasceíte necrotizante (1) Íleo adinâmico (3) Neuropatia (1) Disfunção vesical transitória (1) Fibrilação atrial (1)	15,2	Recidiva: 1,85%

O quadro continua na página seguinte.

		Complicações*			
Autor/ano	**Via (N)**	**Transoperatórias**	**Pós-operatórias**	**Seguimento (meses)**	**Recorrência/ sobrevida**
Ghezzi (2007)	Laparoscopia (50)	Taxa de complicações: 8% Cistostomia (3) Lesão ureteral (1)	Taxa de complicações: 10,4% Fístula ureterovaginal (1) Fístula vesicovaginal (1) Fístula ureteral (1) Obstrução intestinal (1) TVP/EP (1) Linfocisto (2)	10 (2-30)	100% sobrevida
	Laparotomia (48)	Taxa de complicações: 10,4% Transfusão: 4** Cistostomia (2) Lesão de grande vaso (2) Lesão intestinal (1)	Taxa de complicações: 22,9% Reintervenção (1) (sangramento) Hematoma pélvico (1) Hérnia incisional encarcerada (1) Bacteremia/sepse (1) Linfedema (1) Linfocele sintomático (2) Febre de origem desconhecida (2) Infecção e deiscência de sutura (1) Hérnia incisional (1)	58 (32-96)	NI
Ucella (2007)	Laparoscopia (50)	Taxa de complicações: 8% Cistostomia (3) Lesão uretral (1)	Taxa de complicações: 6% Fístula ureteral (2) Fístula vesical (1) Disfunção vesical transitória (7)	NA	NA
	Laparotomia (48)	Taxa de complicações: 4,2% Cistostomias (2)	Taxa de complicações: 0% Disfunção vesical transitória (7)	NA	NA
Diaz-Feijoo (2008)	Laparoscopia (20)	Taxa de complicações: 5% Conversão (1) (falha técnica) 5% Transfusão sanguínea (1) (5%)	Precoce: 0% Transfusão (1) Tardia: 20% Incontinência urinária de stress (2) Evisceração vaginal (3)	22,5 (2-52)	Recidiva: 0 Sobrevida global em 52 meses: 100% Sobrevida livre de doença em 52 meses: 100%
	Laparotomia (30)	Taxa de complicações: 6,67% Coagulação intravascular disseminada com óbito (1) Lesão de ureter (1) Transfusão sanguínea (5) (16,7%)	Precoce: 13% Transfusão (5) Infecção urinária (1) Hematoma de parede abdominal (2) Abscesso de parede abdominal (1) Tardia: 3,3% Incontinência urinária de stress (1)	35 (5-57)	Recidiva: 10% Óbitos: 2 Sobrevida global em 52 meses: 90% Sobrevida livre de doença em 52 meses: 90% 1 óbito por coagulação intravascular disseminada

O quadro continua na página seguinte.

		Complicações*			
Autor/ano	**Via (N)**	**Transoperatórias**	**Pós-operatórias**	**Seguimento (meses)**	**Recorrência/ sobrevida**
Malzoni (2009)	Laparoscopia (65)	Taxa de complicações: 4,62% Cistostomia (1) Enfisema subcutâneo (2)	Disfunção vesical transitória (17) Fistula ureterovaginal (1) Linforreia vaginal (20) Doença febril (6) Transfusão: nenhuma	52,5 (4-89)	Recidiva: 7,69% Sobrevida livre de doença: 92,4%
	Laparotomia (62)	Taxa de complicações: 1,61% Cistostomia (1)	Disfunção vesical (19) Linforreia vaginal (17) Doença febril (8) Transfusão: nenhuma	71,5 (5-151)	Recidiva: 6,4% Taxa de sobrevida: 93,6%
Lee (2011)	Laparoscopia (24)	Transfusão (5) 20,8% Taxa de complicações: 12,5% Conversão (3) 12,5% Lesão de grande vaso (2) Lesão ureteral (1)	Taxa de complicações: 16,7% Infecção do trato urinário (3) Infecção de ferida operatória (1)	78	Sobrevida livre de doença em cinco anos: 90,5% Recidiva: 8,3%
	Laparotomia (48)	Transfusão (23) 47,9%** Taxa de complicações: 14,6% Lesão de grande vaso (3) Lesão ureteral (1) Cistostomia (2)	Taxa de complicações: 16,7% Infecção do trato urinário (3) Infecção de ferida operatória (1) Disfunção vesical transitória (1) Linfedema (1) TVP/EP (1)	75	Sobrevida livre de doença em cinco anos: 93,3% Recidiva: 8,3%

O quadro continua na página seguinte.

		Complicações*			
Autor/ano	**Via (N)**	**Transoperatórias**	**Pós-operatórias**	**Seguimento (meses)**	**Recorrência/ sobrevida**
Nam (2011)	Laparoscopia (263)	Transfusão: 76 (28,9%) Taxa de complicações: 6,8% Cistostomia (9) Lesão ureteral (6) Lesão retal (2) Lesão de grande vaso (2)	Taxa de complicações: 9,2% Morbidade febril (5) Abscesso pélvico (7) Deiscência de sutura (1) Hérnia incisional (3) Perfuração intestinal (1) Fístula do trato urinário (2) Íleo adinâmico (2) Cardiopatia isquêmica (1) Colite pseudomembranosa (1) Lesão do plexo braquial (1) Neuropatia do obturador (1) Estenose ureteral (1) Disfunção vesical (54)	63 (25-150)	Sobrevida global em cinco anos: 94,2% Sobrevida livre de doença em cinco anos: 92,8% Recidiva: 6,08% 11 óbitos
	Laparotomia (263)	Transfusão: 106 (40,3%)** Taxa de complicações: 9,2% Cistostomia (11) Lesão ureteral (3) Lesão do nervo obturador (1)	Taxa de complicações: 21%* Morbidade febril (14) Abscesso pélvico infectado (17) Deiscência de sutura (4) Hérnia incisional (1) Sangramento pós-operatório (1) Fístula do trato urinário (4) Insuficiência renal aguda (1) Íleo adinâmico (7) Colite pseudomembranosa (1) Estenose ureteral (5) Disfunção vesical (52)	127 (26-159)	Sobrevida global em cinco anos: 96,4% Sobrevida livre de doença: 94,4% Recidiva: 5,70% 12 óbitos
Soliman (2011)	Laparoscopia (31)	Transfusão (5) 16% Conversão (5) 16% Taxa de complicações: 16% Lesão de grande vaso (1) Lesão ureteral (2)	TVP/EP (1) Hérnia de portal (1) Infecção de ferida operatória (2) Morbidade febril (1) CTI (3) Pneumonia (2)	NI	NI
	Laparotomia (30)	Transfusão (13) 24%	Morbidade febril (4) Infecção de ferida operatória (4) CTI (3) Pneumonia (2) Abscesso (3) Íleo adinâmico (2)	NI	NI

O quadro continua na página seguinte.

		Complicações*			
Autor/ano	**Via (N)**	**Transoperatórias**	**Pós-operatórias**	**Seguimento (meses)**	**Recorrência/ sobrevida**
Choi (2012)	Laparoscopia (105)	Transfusão (17) 16,19% Taxa de complicações: 5,71% Laceração ureteral (2) Cistostomia (3) Lesão retal (1)	Disfunção vesical transitória (2) Estenose ureteral (3) Linfedema (2) Reinternação (1)	18 (2-59)	Sobrevida livre de doença: 96,4% Recidiva: 2,9%
	Laparotomia (99)	Transfusão (30)** Taxa de complicações: 3,03% Cistostomia (2) Laceração ureteral (1)	Sangramento (2) Infecção de ferida operatória (1) Disfunção vesical (2) Estenose ureteral (3) Reinternação (1)	37 (3-74)	Sobrevida livre de doença: 91,9% Recidiva: NI
	HRVAL (89)	Cistostomia (7) Laceração ureteral (3) Conversão (1) Transfusão (24)	Sangramento (1) Disfunção vesical (1) Estenose ureteral (2) Linfedema (2) Reinternação (2)	29 (4-79)	Sobrevida livre de doença: 92,1% Recidiva: 6,7%
Park (2012)	Laparoscopia (99)	Transfusões: 39,8% Taxa de complicações (4) 4% Lesão de grande vaso (1) 0,6% Lesão intestinal com conversão (1) 0,6% Cistostomia (2) 1,2%	Complicações pós-operatórias (4) 4% Deiscência de sutura (1) 1% Hérnia incisional (1) 1% Íleo adinâmico (1) 1% Estenose ureteral (1) 1% TVP/EP (1) 0,6% Radiculopatia lombossacra (1) 0,6% Disfunção vesical transitória (17) 17,3%	45 3-152 meses	Recidivas: 3% Óbitos: 2 Sobrevida global em cinco anos: 96% Sobrevida livre de doença: 95%
	Laparotomia (159)	Transfusões: 34,3% Taxa de complicações (3)1,9% Lesão de grande vaso (2) Lesão ureteral (1) 0,6%	Complicações pós-operatórias (20) 12,6%* Deiscência de sutura (6) 3,8%* Hérnia incisional (3) 1,9% Íleo adinâmico (4) 2,5% Abscesso pélvico (3) 1,9%* Estenose ureteral (4) 2,5% Fístula urinária (1) 0,6% TVP/EP (4) 2,5% Disfunção vesical (31) 19,5%	45 3-152 meses	Recidivas: 5,7% Óbitos: 7 Sobrevida global em 5 anos: 95% Sobrevida livre de doença em cinco anos: 93%

O quadro continua na página seguinte.

		Complicações*			
Autor/ano	**Via (N)**	**Transoperatórias**	**Pós-operatórias**	**Seguimento (meses)**	**Recorrência/ sobrevida**
Wright (2012)	Laparoscopia (217)	Taxa de complicações: 5,1% Cistostomia (6) Lesão intestinal (4)	Infecção de ferida operatória (3) Abscesso (4) Hemorragia (2) DVT/EP (2) Bacteremia/Sepse (1) Transfusão: 242 (15%)	NI	NI
	Laparotomia (1610)	Taxa de complicações: 5,8% Cistostomia (35) Lesão ureteral (30) Lesão intestinal (2) Lesão vascular (2)	Infecção de ferida operatória (5) Abscesso (23) Hemorragia (28) Obstrução intestinal (3) DVT/EP (13) Bacteremia/Sepse (12) Transfusão: 242 (15%) Óbitos (2) Transfusão: 11 (5,1%)*	NI	NI

Legenda: * Número reflete o número de complicações, algumas pacientes apresentaram mais de uma complicação. ** P < 0,05; NI: não informado; TVP/EP: trombose venosa profunda/embolia pulmonar; CTI: centro de tratamento intensivo; HRVAL: histerectomia radical vaginal assistida por laparoscopia.
Fonte: a autora (2013)

1.8.2 Perda sanguínea e taxa de transfusão

Os autores que estimaram a perda sanguínea durante a histerectomia radical laparoscópica utilizaram técnicas distintas. Alguns usaram a diferença entre o volume total de fluidos aspirado ao final de cirurgia e o volume de fluidos infundido na cavidade abdominal (RAMIREZ, 2006; LI, 2007; MALZONI, 2009; LEE, 2011; CHOI, 2012). Outros estudos consideraram apenas o total de fluidos aspirado da cavidade abdominal (ZAKASHANSKY, 2007). Um estudo estimou a perda sanguínea pela comparação das concentrações de hematócrito e hemoglobina séricos pré e pós-operatórios (DIAZ-FEIJOO, 2008).

Os autores descrevem um volume de perda sanguínea entre 55 mililitros (ml) (MALZONI, 2009) e 619 ml (KIM, 1998). Diversos estudos descreveram uma perda média/mediana de 200 ml (PELLEGRINO, 2009; RAMIREZ, 2006; OBERMAIR, 2003; GHEZZI, 2007; POMEL, 2003). A maioria dos estudos com grupo comparativo descreve um menor volume de sangramento da HRL em comparação a HRA (ABU-RUSTUM, 2003; FRUMOVITZ, 2007; ZAKASHANSKY, 2007; GHEZZI, 2007; DIAZ-

FEIJOO, 2008; MALZONI, 2009; LEE, 2011; NAM, 2011; SOLIMAN, 2011; CHOI, 2012; PARK, 2012). Alguns grupos descreveram uma menor taxa de transfusão (ZAKASHANSKY, 2007; GHEZZI, 2007; NAM, 2011; SOLIMAN, 2011; LEE, 2011; CHOI, 2012). Um estudo comparativo não encontrou diferença no volume de sangramento (LI, 2007).

As taxas de transfusão descritas nos estudos citados nos Quadros 7 e 9 estão entre 1,3% (SPIRTOS, 2002) e 39,8% (PARK, 2012). Alguns estudos descrevem séries sem nenhuma transfusão para as pacientes submetidas à HRL (SPIRTOS, 1996b; ZAKASHANSKY, 2007; PUNTAMBEKAR, 2007; GHEZZI, 2007; MALZONI, 2009). Hong *et al.* (2012) descreveram uma taxa de transfusão sanguínea muito superior a dos outros estudos (65,2%), e os autores justificaram o achado por terem realizado linfadenectomia para-aórtica em 72% das pacientes. Nos três estudos de caso-controle citados, as taxas de transfusão foram significativamente menores no grupo submetido à HRL, em comparação ao grupo submetido à HRA (Quadro 9) (ZAKASHANSKY, 2007; LEE, 2011; NAM, 2011).

1.8.3 Tempo de internação

Os estudos citados nos Quadros 6 e 8 descrevem um tempo de internação entre um dia (RAMIREZ, 2006; CANTON-ROMERO, 2010) e 13 dias (LI, 2007; YAN, 2011; NAM, 2011) para a histerectomia radical laparoscópica. Nos três estudos de caso-controle citados, o tempo de internação foi significativamente menor no grupo submetido à HRL, em comparação ao grupo submetido à HRA (Quadro 8) (ZAKASHANSKY, 2007; LEE, 2011; NAM, 2011). Outros estudos também encontraram resultados semelhantes (ABU-RUSTUM, 2003; FRUMOVITZ, 2007; GHEZZI, 2007; DIAZ-FEIJOO, 2008; MALZONI, 2009; SOLIMAN, 2011; PARK, 2012; WRIGHT. 2012).

1.8.4 Radicalidade cirúrgica

Uma das maiores preocupações na transposição das técnicas oncológicas abdominais para laparoscopia é com a radicalidade da cirurgia. Os primeiros autores a propor desfechos histopatológicos intermediários que avaliassem a radicalidade cirúrgica foram Spirtos *et al.*, em 1996. Esses autores propuseram que, além do

número de linfonodos excisados, as medidas dos paramétrios e do manguito vaginal fossem utilizadas como parâmetros de radicalidade cirúrgica da histerectomia radical laparoscópica (SPIRTOS, 1996b).

1.8.5 Linfonodos pélvicos

Os estudos citados nos Quadros 6 e 8 descrevem um número de linfonodos pélvicos retirados entre 13 (POMEL, 2003; RAMIREZ, 2006) e 34 (SPIRTOS, 2002; NAM, 2011). Publicação recente de 2009 da Organização Europeia de Pesquisa e Tratamento do Câncer propõe que o número de mínimo de linfonodos pélvicos excisados seja de 11 (VERLEYE, 2009). Alguns estudos com grupo controle descrevem um número similar de linfonodos pélvicos excisados nas pacientes submetidas à HRL e à HRA (ABU-RUSTUM, 2003; LI, 2007; GHEZZI, 2007; DIAZ-FEIJOO, 2008; LEE, 2011; CHOI, 2012; PARK, 2012) e um número similar de linfonodos positivos (LI, 2007; DIAZ-FEIJOO, 2008; GHEZZI, 2007; ZAKASHANSKY, 2007; LEE, 2011; CHOI, 2012). Contudo outros estudos descrevem um número menor de linfonodos pélvicos excisados pela HRL (FRUMOVITZ, 2007; MALZONI, 2009). Em dois dos três estudos de caso-controle, o número de linfonodos pélvicos excisados foi significativamente maior no grupo laparoscópico (NAM, 2011; ZAKASHANSKY, 2007).

1.8.6 Linfonodos para-aórticos

Spirtos *et al.* (1996b) descreveram uma série de casos de 10 pacientes que realizaram histerectomia pélvica e para-aórtica. A média de linfonodos para-aórticos excisados foi de 6,5. Em estudo subsequente, o mesmo autor descreveu uma média de 10,3 linfonodos para-aórticos excisados (78 pacientes) (SPIRTOS, 2002). Hong *et al.* (2012) realizaram linfadenectomia para-aórtica em 72% das pacientes, sendo que o número médio de linfonodos retirados foi sete (1-39). Xu *et al*. (2007) descreveram a realização de linfadenectomia para-aórtica nas pacientes nos estádio IB2 e II, o que correspondeu a 45,69% (143 pacientes) da amostra. Os autores não descreveram nem o *status* nem o número de linfonodos excisados (XU, 2007). No estudo publicado por Nam *et al.* (2011), 35% das pacientes submetidas à HRL e 38,4% das pacientes submetidas à HRA foram submetidas à amostragem de

linfonodos para-aórticos (p = 0,402). O número de linfonodos para-aórticos excisados não diferiu entre os grupos (3,1 *vs.* 3,3; p = 0,367). O número de linfonodos para-aórticos positivos também não foi diferente entre os grupos (NAM, 2011).

1.8.7 Paramétrios e manguito vaginal

O Quadro 10 apresenta os estudos sem grupo controle e controlados que descreveram medidas dos paramétrios e do manguito vaginal na peça anatomopatológica.

Quadro 10 – Medidas dos paramétrios e manguito vaginal das peças anatomopatológicas da histerectomia radical laparoscópica: estudos controlados e não controlados

Autor/ano	Via (N)	Paramétrio direito (cm)	Paramétrio esquerdo (cm)	Manguito vaginal (cm)
Spirtos (1996b)	HRL (10)	3,3*	-	2,15
Puntambekar (2007)	HRL (248)	-	-	3,5
Ghezzi (2007)	HRL (50) HRA (48)	3,3 3,1	3,3 3,5	-
Frumovitz (2007)	HRL (35) HRA (54)	3,7 3,7	3,8 3,7	1,7 1,9
Canton-Romero (2010)	HRL (54)	2,25*	-	2,4
Soliman (2011)	HRL (31) HRA (30)	3,0 3,6	3,3 3,5	2,1 1,9
Choi (2011)	HRL (105) HRA (99)			1,8 2,1

Legenda: * autores que informaram apenas o tamanho médio de ambos os paramétrios; cm: centímetros.
Fonte: a autora (2013)

1.8.8 Complicações transoperatórias

As complicações transoperatórias dos estudos não controlados estão descritas no Quadro 7, e dos estudos controlados, no Quadro 9. As taxas de complicações transoperatórias oscilaram entre 4% (POMEL, 2003; GIL-MORENO, 2005; XU, 2007; MALZONI, 2009; CANTON-ROMERO, 2010; PARK, 2012) e 16% (SOLIMAN, 2011). Outros três estudos têm taxa de complicações transoperatórias superiores a 10% (ABU-RUSTUM, 2003; FRUMOVITZ, 2007; LEE, 2011). As

complicações foram mais frequentes nas cirurgias iniciais (OBERMAIR, 2003; LI, 2007; XU, 2007; UCELLA, 2007; HONG, 2012). A maioria dos estudos descreve conversões da histerectomia radical laparoscópica em histerectomia radical aberta (SPIRTOS, 2002; ABU-RUSTUM, 2003; OBERMAIR, 2003; LI, 2007; XU, 2007; FRUMOVITZ, 2007; DIAZ-FEIJOO, 2008; PELLEGRINO, 2009; SOLIMAN, 2011; YAN, 2011; LEE, 2011), cujas taxas oscilaram entre 1% (XU, 2007; YAN, 2011; PARK, 2012) e 16% (SOLIMAN, 2011).

Os motivos para a conversão da cirurgia são laceração de grande vaso (SPIRTOS, 2002; OBERMAIR, 2003; ABU-RUSTUM, 2003; LI, 2007; XU, 2007; FRUMOVITZ, 2007; LEE, 2011; YAN, 2011), lesão de bexiga (SPIRTOS, 2002; ABU-RUSTUM, 2003; LI, 2007; YAN, 2011), lesão ureteral (LEE, 2011; YAN, 2011), lesão de cólon e reto (XU, 2007; PARK, 2012), dificuldade para manter pneumoperitônio ou problemas no equipamento (SPIRTOS, 2002; GIL-MORENO, 2005), colocação de *stents* ureterais (SPIRTOS, 2002), lesão de nervo obturador (PELLEGRINO, 2009), aderências (PELLEGRINO, 2009; NAM, 2011) e hipercapnia (XU, 2011; NAM, 2011). À exceção de dificuldade para manter pneumoperitônio e dificuldades técnicas com o equipamento específico, as outras complicações não são exclusivas da abordagem laparoscópica.

A laceração involuntária de bexiga é a complicação transoperatória mais comumente descrita (SPIRTOS, 2002; POMEL, 2003; ABU-RUSTUM, 2003; RAMIREZ, 2006; GHEZZI, 2007; LI, 2007; ZAKASHANSKY, 2007; PUNTAMBEKAR, 2007; XU, 2007; UCELLA, 2007; FRUMOVITZ, 2007; PELLEGRINO, 2009; MALZONI, 2009; NAM, 2011; SOLIMAN, 2011; YAN, 2011; HONG, 2012; CHOI, 2012; WRIGHT, 2012; PARK, 2012). Os autores descrevem taxas entre 0,93% (PELLEGRINO, 2009) e 8,74% (HONG, 2012). Em estudo de caso-controle que comparou as taxas de lesão vesical não houve diferença estatisticamente significativa entre as pacientes submetidas à HRL (263) e à HRA (263) – 3,4% *vs.* 4,2% (p = 0,815) (NAM, 2011). Outro estudo comparou as taxas de lesão vesical e não encontrou diferença estatisticamente significativa entre as pacientes submetidas à HRL (217) e à HRA (1.610) – 2,8% *vs.* 2,2% (p = 0,79) (WRIGHT, 2012).

Os estudos também descrevem lesões de ureter (SPIRTOS, 2002; ABU-RUSTUM, 2003; PUNTAMBEKAR, 2007; GHEZZI, 2007; UCELLA, 2007; LEE, 2011; NAM, 2011; SOLIMAN, 2011; YAN, 2011; CHOI, 2012; HONG, 2012), cujas taxas oscilam entre 0,40% (PUNTAMBEKAR, 2007; YAN, 2011) e 6,45% (SOLIMAN,

2011). Alguns autores descreveram o manejo com sutura primária de ureter pela via laparoscópica (PUNTAMBEKAR, 2007; UCELLA, 2007; SOLIMAN, 2011; CHOI, 2012; HONG, 2012) ou passagem de cateter JJ (SPIRTOS, 2002; YAN, 2011). Estudo de caso-controle que comparou as taxas de lesão ureteral não encontrou diferença estatisticamente significativa entre as pacientes submetidas à HRL (263) e à HRA (263) – 2,8% *vs.* 2,2% (p = 0,79); 2,3% *vs.* 1,1% (p = 0,508) (NAM, 2011).

As lesões de grande vaso são frequentemente descritas (SPIRTOS, 2002; ABU-RUSTUM, 2003; OBERMAIR, 2003; FRUMOVITZ, 2007; LI, 2007; PUNTAMBEKAR, 2007; XU, 2007; LEE, 2011; NAM, 2011; YAN, 2011; SOLIMAN, 2011; HONG, 2012; PARK, 2012). Os autores descrevem taxas de lesão de grande vaso entre 0,76% (RAMIREZ, 2006) e 8,57% (FRUMOVITZ, 2007; LEE, 2011). Os vasos mais comumente lesados são veia ilíaca interna (OBERMAIR, 2003; GHEZZI, 2007; LI, 2007; XU, 2007; LEE, 2011), artéria mesentérica inferior (SPIRTOS, 2002; XU, 2007), veia cava (SPIRTOS, 2002; HONG, 2012) e veia ilíaca externa (XU, 2007; FRUMOVITZ, 2007; GHEZZI, 2007). As lesões de grande vaso foram manejadas laparoscopicamente com a colocação de grampos endoscópicos (PUNTAMBEKAR, 2007; XU, 2007) ou sutura primária de vaso (LI, 2007; PUNTAMBEKAR, 2007; XU, 2007; YAN, 2011; NAM, 2011; SOLIMON, 2011; HONG, 2012). Estudo de caso-controle comparou as taxas de grande vaso e não encontrou diferença estatisticamente significativa entre as pacientes submetidas à HRL (263) e HRA (263) – 0,8% *vs*. 0 (p = 1,0) (NAM, 2011).

Alguns estudos descreveram laceração intestinal (POMEL, 2003; XU, 2007; CANTON-ROMERO, 2010; PARK, 2012; WRIGHT, 2012) ou retal (PUNTAMBEKAR, 2007; NAM, 2011; CHOI, 2012; PARK, 2012), com frequência entre 0,8% (PUNTAMBEKAR, 2007; NAM, 2011) e 5,55% (CANTON-ROMERO, 2010). Estudo comparou as taxas de lesão intestinal e encontrou uma diferença estatisticamente significativa entre as pacientes submetidas à HRL (217) e à HRA (1610) – 1,8 *vs.* 0,4% (p = 0,02) (WRIGHT, 2012).

As lesões de nervo obturador são eventos raramente descritos (YAN, 2011; PELLEGRINO, 2009; OBERMAIR, 2003). Os autores descreveram o manejo da complicação com sutura laparoscópica no mesmo procedimento cirúrgico, apresentando boa evolução pós-operatória (PELLEGRINO, 2009; YAN, 2011). Obermair (2003) descreveu uma lesão de nervo obturador na qual a paciente evoluiu para dor severa irresponsiva ao manejo. Dezessete meses depois da HRL, a

paciente foi submetida à neurólise do nervo por laparotomia, com boa evolução (OBERMAIR, 2003).

Os estudos que compararam a taxa global de complicações transoperatórias entre a HRL e a HRA encontraram diferença estatisticamente significativa entre os grupos (LI, 2007; GHEZZI, 2007; UCELLA, 2007; SOLIMAN, 2011; LEE, 2011; NAM, 2011; PARK, 2012; WRIGHT, 2012).

1.8.9 Complicações pós-operatórias

As taxas de complicações pós-operatórias dos estudos não controlados estão descritas no Quadro 7, e as dos estudos controlados, no Quadro 9, oscilando entre 4% (PARK, 2012) e 40% (LI, 2007). Alguns estudos descrevem uma diminuição nas taxas de complicações pós-operatórias ao longo do tempo (OBERMAIR, 2003; UCELLA, 2007; LI, 2007; HONG, 2012). Um único estudo descreveu ausência de complicações (SPIRTOS, 1996b).

As complicações relacionadas à dissecção do ureter são frequentemente descritas. Entre elas estão a estenose (KIM, 1998; POMEL, 2003; XU, 2007; PELLEGRINO, 2009; NAM, 2011; CHOI, 2012; PARK, 2012) e as fístulas ureterais (KIM, 1998; SPIRTOS, 2002; LI, 2007; PUNTAMBEKAR, 2007; XU, 2007; GHEZZI, 2007; UCELLA, 2007; PELLEGRINO, 2009; MALZONI, 2009; YAN, 2011; NAM, 2011). As taxas de estenose ureteral oscilaram entre 0,3% (XU, 2007; NAM, 2011) e 5,56% (KIM, 1998). Nos estudos citados, as pacientes foram tratadas com passagem de cateteres JJ (XU, 2007; PELLEGRINO, 2009; CHOI, 2012) ou cirurgicamente (POMEL, 2003; PELLEGRINO, 2009). As taxas de fístula ureteral oscilaram entre 0,83% (YAN, 2011; NAM, 2011) e 5,56% (KIM, 1998). As fístulas foram tratadas com a passagem de cateteres JJ (PUNTAMBEKAR, 2007; XU, 2007; GHEZZI, 2007; UCELLA, 2007; PELLEGRINO, 2009; MALZONI, 2009; YAN, 2011) ou cirurgicamente (PELLEGRINO, 2009; XU, 2007; UCELLA, 2007; PUNTAMBEKAR, 2007).

Os estudos descrevem fístulas vesicovaginais (OBERMAIR, 2003; POMEL, 2007; LI, 2007; XU, 2007; GHEZZI, 2007; UCELLA, 2007; MALZONI, 2009; YAN, 2011), cujas taxas se situam abaixo de 2% (KIM, 1998; OBERMAIR, 2003; XU, 2007; GHEZZI, 2007; LI, 2007) e que podem ser tratadas conservadoramente (UCELLA, 2007; XU, 2007; YAN, 2011) ou com cirurgia (OBERMAIR, 2003; POMEL, 2007; XU,

2007; GHEZZI, 2007). Um estudo entre os citados no Quadro 7 descreveu um caso de fístula retovaginal, tratada inicialmente com colostomia, que foi revertida quatro meses após a HRL (OBERMAIR, 2003).

Alguns estudos descrevem casos de obstrução intestinal (OBERMAIR, 2003; LI, 2007; GHEZZI, 2007; YAN, 2011; HONG, 2012) e as taxas de taxas de obstrução intestinal variaram entre 0,4% (YAN, 2011) e 2% (LI, 2007). Linfocele costuma ter manejo expectante (SPIRTOS, 2002; OBERMAIR, 2003; RAMIREZ, 2006; XU, 2007; LI, 2007; GHEZZI, 2007; CANTON-ROMERO, 2010; YAN, 2011; HONG, 2012). Os estudos também descrevem linfedema de membros inferiores (KIM, 1998; OBERMAIR, 2003; XU, 2007; YAN, 2011; HONG, 2012; CHOI, 2012). Um único estudo descreveu casos de linforreia durante o exame vaginal, tanto entre as pacientes submetidas à HRL (30,76%) quanto entre as pacientes submetidas à HRA (26,98%) (MALZONI, 2009).

Alguns estudos descreveram deiscência de sutura da cúpula vaginal (DIAZ-FEIJOO, 2008; POMEL, 2003; RAMIREZ, 2006; PELLEGRINO, 2009; CANTON-ROMERO, 2010; NAM, 2011; PARK, 2012), com taxas que oscilaram entre 1,88% (PARK, 2012) e 15% (DIAZ-FEIJOO, 2008). Deiscência ou evisceração pelos portais dos trocartes é uma complicação incomum (POMEL, 2003; NAM, 2011; SOLIMAN, 2011; PARK, 2012). Raros estudos descrevem situações de sangramento pós-operatório com necessidade de reintervenção cirúrgica (PUNTAMBEKAR, 2007; NAM, 2011; WRIGHT, 2012). Outra complicação incomum é dor no trajeto do nervo obturador (POMEL, 2003; OBERMAIR, 2003; XU, 2007; FRUMOVITZ, 2007; NAM, 2011), que costuma apresentar regressão espontânea nos seis meses seguintes da cirurgia (XU, 2007).

Entre as complicações clínicas mais frequentemente descritas está a trombose venosa profunda/embolia pulmonar (TVP/EP) (SPIRTOS, 2002; OBERMAIR, 2003; RAMIREZ, 2006; ZAKASHANSKY, 2007; FRUMOVITZ, 2007; XU, 2007; GHEZZI, 2007; SOLIMAN, 2011; WRIGHT, 2012; PARK, 2012). As taxas oscilaram entre 0,64% (XU, 2007) e 8,57% (FRUMOVITZ, 2007). Um estudo descreveu um óbito associado à TVP/EP (OBERMAIR, 2003). Estudo que comparou 217 pacientes submetidas à HRL e 1.410 pacientes submetidas à HRA descreveu uma diferença estatisticamente significativa nas taxas de complicações clínicas entre os grupos (3,2 *vs.* 8,8%, respectivamente; p = 0,01), que incluíram trombose venosa profunda, parada cardíaca, insuficiência respiratória, insuficiência renal,

bacteremia/sepse, choque, pneumonia. Nenhum dos desfechos clínicos atingiu significância estatística isoladamente. Houve dois óbitos entre as pacientes submetidas à HRA (WRIGHT, 2012).

Diversos estudos descreveram complicações infecciosas (KIM, 1998; SPIRTOS, 2002; ABU-RUSTUM, 2003; POMEL, 2003; OBERMAIR, 2003; GIL-MORENO, 2005; ZAKASHANSKY, 2007; PUTAMBEKAR, 2007; FRUMOVITZ, 2007; PELLEGRINO, 2009; MALZONI, 2009; LEE, 2011; SOLIMAN, 2011; NAM, 2011; WRIGHT, 2012), que oscilaram entre 1,3% (SPIRTOS, 2002; PUNTAMBEKAR, 2007) e 25,8% (SOLIMAN, 2011). As infecções do trato urinário estão entre as complicações infecciosas mais frequentemente descritas entre as pacientes submetidas à HRL (SPIRTOS, 2002; OBERMAIR, 2003; POMEL, 2003; GIL-MORENO, 2005; PUTAMBEKAR, 2007; LEE, 2011). Estudo que comparou as taxas de morbidade infecciosa entre a HRL (35) e a HRA (54) descreveu uma taxa significativamente menor para as pacientes submetidas à HRL (53% *vs.* 18 %; p = 0,001) (FRUMOVITZ, 2007). No estudo posterior do mesmo grupo de pesquisa, em que foram comparadas 31 pacientes submetidas à HRL e 30 pacientes submetidas à HRA, as taxas de morbidade infecciosa foram significativamente menores para as pacientes submetidas à HRL (25,8% *vs.* 53,33%; p < 0,01) (SOLIMAN, 2011). Estudo de caso-controle que comparou as taxas de morbidade infecciosa entre a HRL (24) e a HRA (48) não encontrou diferença estatisticamente significativa entre os grupos (16,7% *vs.* 14,6; p > 0,05) (LEE, 2011).

Disfunção vesical foi a complicação pós-operatória mais comumente descrita (KIM, 1998; SPIRTOS, 2002; POMEL, 2003; OBERMAIR, 2003; GIL-MORENO, 2005; ZAKASHANSKY, 2007; LI, 2007; PUNTAMBEKAR, 2007; XU, 2007; GHEZZI, 2007; UCELLA, 2007; PELLEGRINO, 2009; MALZONI, 2009; CANTON-ROMERO, 2010; NAM, 2011; CHOI, 2012; HONG, 2012; PARK, 2012) e a sua frequência oscilou entre 2% (XU, 2007; PUNTAMBEKAR, 2007; HONG, 2012; CHOI, 2012) e 32,22% (LI, 2007). Na maioria dos estudos, houve retorno do esvaziamento vesical normal até seis meses após a HRL (KIM, 1998; OBERMAIR, 2003; POMEL, 2003; XU, 2007; PUNTAMBEKAR, 2007; GHEZZI, 2007; PELLEGRINO, 2009; CANTON-ROMERO, 2010; HONG, 2012). Alguns estudos descreveram casos de disfunção vesical permanente, em que as pacientes necessitaram realizar autossondagem definitivamente (SPIRTOS, 2002; GIL-MORENO, 2005). Outros descreveram incontinência urinária consequente a disfunção vesical (DIAZ-FEIJOO, 2008; GIL-

MORENO, 2005). Nos estudos que compararam as taxas de disfunção da HRL e da HRA, não houve diferença estatisticamente significativa entre os grupos (LI, 2007; UCELLA, 2007; NAM, 2011; PARK, 2012).

Alguns estudos que realizaram a comparação na taxa global de complicações pós-operatórias entre as pacientes submetidas à HRL e à HRA descreveram taxas similares entre os grupos (UCELLA, 2007; LI, 2007; ZAKASHANSKY, 2007; WRIGHT, 2012). Estudo de caso-controle comparou 263 pacientes submetidas à HRL e 263 pacientes à HRA, e a taxa de complicações foi estatisticamente menor no grupo submetido à laparoscopia (9,2% *vs.* 21%; p < 0,001). As diferenças entre as taxas de abscesso pélvico/linfocele infectados (2,7 *vs.* 6,5; p = 0,052) foram próximas da significância estatística (NAM, 2011).

Estudo incluiu apenas pacientes com idade igual ou superior a 65 anos, comparando 99 pacientes submetidas à HRL e 159 pacientes submetidas à HRA. O grupo laparoscópico apresentou uma taxa de complicações significativamente menor (4,2% *vs.* 12,6%; p = 0,026). Houve diferença estatisticamente significativa nas taxas de: deiscência de sutura (1% *vs.* 3,8%; p = 0,014) e abscessos pélvicos (0 *vs.* 1,9%; p = 0,055) (PARK, 2012).

1.8.10 Sobrevida

Os dados referentes à sobrevida dos estudos sem grupo controle estão descritos no Quadro 7, os dos estudos controlados, no Quadro 9. Nos estudos com grupo controle em que as análises foram realizadas, não houve diferença estatisticamente significativa nas taxas de recidiva (LI, 2007; PARK, 2012), sobrevida global (DIAZ-FEIJOO, 2008; MALZONI, 2009; NAM, 2011; PARK, 2012) e sobrevida livre de doença (DIAZ-FEIJOO, 2008; LEE, 2011; MALZONI, 2009; NAM, 2011; CHOI, 2012; PARK, 2012) entre as pacientes submetidas à histerectomia radical laparoscópica e à histerectomia radical aberta. No estudo em que a HR foi calculada, não houve diferença nos riscos de recidiva (HR 1,28; IC 95%: 0,62-2,64) ou óbito (HR: 1,46; IC 95%: 0,62-3,43) (NAM, 2011). Os estudos descrevem tempos de seguimento para as pacientes submetidas à histerectomia radical laparoscópica desde 7,2 meses (GHEZZI, 2007) até 78 meses (LEE, 2011). Na maioria dos estudos, o tempo de seguimento das pacientes submetidas à HRL foi menor do que

o das pacientes que realizaram HRA (ZAKASHANSKY, 2007; FRUMOVITZ, 2007; GHEZZI, 2007; DIAZ-FEIJOO, 2008; NAM, 2011; CHOI, 2012).

Estudo de caso-controle comparou 30 pacientes submetidas à HRL e 30 pacientes submetidas à HRA nos estádios IA2-IIA. As pacientes foram pareadas por idade, estádio da FIGO, tipo histológico e comprometimento linfonodal. Três pacientes no grupo laparoscópico e duas pacientes no grupo submetido à laparotomia apresentaram linfonodos positivos. Dez pacientes em cada grupo foram submetidas à quimiorradioterapia adjuvante devido a comprometimento linfonodal, margens exíguas e fatores de risco histopatológicos intermediários. Uma paciente do grupo HRA apresentou metástase em ferida operatória, ressecada cirurgicamente. Ao final do seguimento, todas as pacientes estavam vivas. A mediana no tempo de seguimento no grupo laparoscópico foi de 20 meses e no grupo laparotômico foi de 41 meses (ZAKASHANSKY, 2007).

Estudo de caso-controle publicado em 2011 comparou 24 pacientes submetidas à HRL e 48 pacientes submetidas à HRA e incluiu pacientes entre os estádios IA2-IIA. Os controles foram pareados por idade, estádio da FIGO, subtipo histológico e cirurgião. Quatro pacientes no grupo submetido à HRL (16,7%) e 10 pacientes no grupo submetido à HRA (20%) apresentaram linfonodos pélvicos positivos ($p > 0,05$). Sete pacientes no grupo laparoscópico (29,2%) e 13 pacientes no grupo laparotômico (27,1%) receberam radioterapia ou quimiorradioterapia adjuvante ($p > 0,05$). A mediana do tempo de seguimento foi de 78 e 75 meses, respectivamente. A taxa de recidiva foi de 8,3% para ambos os grupos. A sobrevida livre de doença em cinco anos foi de 90,5% e 93,3%, respectivamente ($p = 0,918$) (LEE, 2011).

Estudo de caso-controle comparou 263 pacientes submetidas à HRL e 263 pacientes submetidas à HRA pareadas por metástases linfonodais, envolvimento parametrial, profundidade da invasão estromal profunda, tamanho tumoral, IELV e idade. Não houve diferença estatisticamente significativa na proporção de pacientes submetidas à linfadenectomia para-aórtica (35% *vs.* 38,4%; $p = 0,402$); e 19% das pacientes no grupo submetido à HRL e 17,1% das pacientes no grupo submetido à HRA fizeram tratamento adjuvante ($p = 0,78$). A mediana do tempo de seguimento foi de 63 meses (25-150) para a HRL e 127 meses (26-159) para a HRA. Ao menos 53% das sobreviventes submetidas à HRL e 85,3% das sobreviventes submetidas à HRA foram acompanhadas por 60 meses ($p < 0,001$). Dezesseis pacientes no grupo

laparoscópico (6,08%) e 15 no grupo laparotômico (5,7%) recidivaram (p = 1,0); 12 pacientes no grupo laparoscópico (4,56%) e 11 pacientes no grupo laparotômico (4,18%) foram a óbito (p = 1,0). Não houve diferença nos riscos de recidiva (HR: 1,28; IC 95%: 0,62-2,64) ou óbito (HR: 1,46: IC 95%: 0,62-3,43). Mesmo para tumores maiores de 2 cm, os riscos de recidiva (HR: 0,82; IC 95%: 0,31-2,16) ou óbito (HR: 1,01; IC 95%: 0,35-2,95) não diferiram entre as pacientes submetidas à HRL e à HRA. A sobrevida livre de recidiva em cinco anos foi de 92,8% e 94,4%, respectivamente (p = 0,499), e a sobrevida global foi de 95,2% *vs.* 96,4% (p = 0,451) (NAM, 2011).

Estudo retrospectivo sem grupo controle incluiu 118 pacientes submetidas à HRL nos estádios IA2-IIA. A linfadenectomia para-aórtica foi realizada em 72% dos casos. As pacientes só não eram submetidas à linfadenectomia para-aórtica se o tumor fosse estádio IA2 ou IB1 ≤ 2 cm, sem metástases em linfonodos pélvicos. Se o tumor fosse IB1 > 2 cm e sem metástases em linfonodos pélvicos, a linfadenectomia era estendida até o nível da artéria mesentérica inferior; e se o tumor fosse IB1 e tivesse linfonodos positivos, ou se fosse IB2 ou mais avançado, independentemente do *status* linfonodal, a linfadenectomia era estendida até a veia renal. Setenta e três por cento das pacientes tinham pelo menos um fator de risco histopatológico intermediário ou alto, e 28 pacientes (23,8%) tiveram linfonodos positivos. Trinta e uma pacientes (35,6%) receberam radioterapia adjuvante, e 36 (41,3%) foram submetidas à quimiorradioterapia adjuvante. Na regressão de Cox, apenas as metástases linfonodais foram o único fator, independentemente de mau prognóstico (HR: 7,0; p = 0,022). A taxa de recidiva nesse estudo foi de 6,78%. A mediana do tempo de seguimento foi de 31 meses (1-89 meses). A sobrevida livre de doença em cinco anos foi de 90%, e a sobrevida global foi de 89% (HONG, 2012).

Em estudo publicado recentemente, 240 pacientes nos estádios IA2, IB1, IB2, IIA e IIB foram submetidas à HRL. Excluindo as perdas, a mediana do tempo de seguimento de 211 pacientes foi de 35 meses (2-125 meses). Oitenta e sete pacientes (39,4%) tinham pelo menos um fator histopatológico de alto risco e fizeram radioterapia adjuvante, sendo que 25 delas fizeram quimioterapia concomitante. Trinta e oito pacientes (24,17%) recidivaram ou apresentaram metástases. A sobrevida em cinco anos foi de 100%, 82%, 66% e 60%, respectivamente. Cinquenta e oito pacientes (24,17%) apresentaram linfonodos pélvicos comprometidos. Considerando as pacientes com linfonodos positivos em todos os

estádios, a sobrevida global em cinco anos foi de 59%, e sem linfonodos positivos a sobrevida foi de 84% ($p < 0,01$). A sobrevida global em cinco anos no estádio IB1 com linfonodos positivos foi de 59%, e com linfonodos negativos foi de 88% ($p < 0,01$). Na regressão proporcional de Cox, somente metástases linfonodais (OR: 3,83; $p < 0,05$) foram um fator independente de mau prognóstico. A sobrevida global em cinco anos no estádio IB1 para tumores maiores de 4 cm foi de 76%, e para tumores menores de 4 cm foi de 89% ($p = 0,28$) (YAN, 2011).

1.9 DOR PÓS-OPERATÓRIA

Indivíduos que vão à cirurgia apresentam dor no período pós-operatório mesmo quando a administração de analgésicos opioides e não opioides é otimizada (BRENNAN, 2011) ou quando são utilizadas técnicas de anestesia regional (WU, 2011). Após a lesão tissular cirúrgica, a ativação simpática e neuroendócrina, em conjunto com dor pós-operatória não controlada, pode levar a respostas fisiológicas potencialmente deletérias, como taquicardia, hipertensão, hipoglicemia, imunossupressão, estase venosa, agregação plaquetária (WU, 2011), *delirium* (LYNCH, 1998) e ao desenvolvimento de dor crônica (PINTO, 2012b). Para pacientes com muitas comorbidades, reservas fisiológicas diminuídas ou aqueles submetidos a procedimentos cirúrgicos de maior risco, esses fenômenos podem aumentar possibilidade de complicações, embora não esteja estabelecido se o tratamento efetivo da dor possa interferir no desfecho cirúrgico global do paciente (WU, 2011). Entretanto doses maiores de opioides reduzem a dor à custa de aumento dos efeitos colaterais como náusea, vômito, íleo adinâmico, depressão respiratória e sedação (BRENNAN, 2011).

Para pacientes submetidos a procedimentos cirúrgicos maiores, dor em repouso e em movimento são sintomas comuns. A dor em repouso é geralmente moderada e desaparece na primeira semana após a cirurgia. A dor para movimentação é em geral severa e pode persistir por semanas. A capacidade funcional do paciente pode ser limitada para atividades como tossir ou caminhar (BRENNAN, 2011). Estudo delineado para determinar os pontos de corte para dor moderada ou severa, utilizando a Escala Verbal Numérica (EVN), incluiu 435 pacientes submetidos a procedimentos cirúrgicos (cirurgias geral, de trauma e

maxilofacial). Os autores descreveram como o ponto de corte para dor moderada-severa um valor na EVN ≥ 4 (GERBASHAGEN, 2011).

Existem dois grandes componentes na dor perioperatória: a dor inflamatória e a dor neuropática, que compartilham muitas características e podem ser experienciadas conjuntamente ou em separado. Após a incisão, o estímulo nociceptivo provoca a liberação de substâncias inflamatórias no tecido afetado, que leva à sensibilização da inervação, causando um fenômeno conhecido como sensibilização periférica (CHANDRAKANTAN, 2011). Alguns estudos sugerem atividade espontânea dos receptores nociceptivos após a incisão (BRENNAN, 2011) e receptores mecanicamente silentes passariam à atividade após a incisão cirúrgica (WU, 2011). Tanto hiperalgesia tátil quanto térmica estão presentes (BRENNAN, 2011; WU, 2011).

A chegada dos impulsos aferentes ao sistema nervoso central provoca a sensibilização do sistema, fenômeno conhecido como sensibilização central. Ambas as formas de sensibilização são mediadas por muitos neurotransmissores e sistemas de retroalimentação, sendo protetores por natureza. Em geral, assim que o tecido cicatriza, a liberação de substância inflamatória cessa (CHANDRAKANTAN, 2011).

A dor neuropática pós-operatória é provavelmente a causa mais importante da pós-operatória persistente e é causada pela lesão direta dos nervos envolvidos no campo cirúrgico. O componente neuropático da dor pode se desenvolver e persistir na ausência de estímulo nocivo ou inflamação periférica. Por conseguinte, técnicas cirúrgicas que diminuam o dano aos nervos devem ser utilizadas sempre que possível. Tanto a dor aguda quanto a dor crônica se expressam em um substrato complexo, fisiológico, genético e psicossocial, que contribui não só para a conversão da atividade somatossensorial na experiência dolorosa, mas na amplitude e na reação à sensação e também nas mudanças de humor e comportamento relacionadas (KEHLET, 2006).

A avaliação factível e confiável da dor é essencial para a condução de estudos científicos e para o manejo dos pacientes. A dor aguda pode ser confiavelmente avaliada por ferramentas unidimensionais, como a Escala Visual Analógica (EVA) de 10 pontos e a Escala Verbal Numérica (EVN) de 10 pontos (DELOACH, 1986; JENSEN, 2002), e seu melhor funcionamento ocorre para expressar a sensação subjetiva de dor no momento presente (BREIVIK, 2008).

Ambas mostraram valores muito próximos em seus escores para o mesmo paciente ao longo do tempo (DELOACH, 1986; BREIVIK, 2008), e a utilização de mais de uma escala não aumenta a sensibilidade para detectar as modificações da dor ao longo do tempo (JENSEN, 2002). A Escala Verbal Categórica é considerada menos acurada do que a EVN e a EVA (BREIVIK, 2008; AUBRUN, 2008). Uma das limitações das escalas com EVA ou EVN é que elas partem do pressuposto de que dor e ansiedade são experiências unidimensionais (AUBRUN, 2008).

Alguns estudos avaliaram fatores de risco associados à presença de dor pós-operatória severa. Estudo publicado em 2003 seguiu uma coorte de 1.413 pacientes submetidos a várias cirurgias, com exceção de neurocirurgia e cirurgia cardíaca. Os autores consideraram como dor pós-operatória severa um escore na EVN ≥ 8 na primeira hora pós-operatória. Trezentos e sessenta e seis pacientes (26,8%) apresentaram dor severa. Os fatores pré-operatórios preditores de dor severa pós-operatória foram idade, sexo feminino, incisão ≥ 10 cm, dor pré-operatória e ansiedade (KALKMAN, 2003).

Entre os componentes psicológicos associados à dor pós-operatória após a realização de histerectomia está a ansiedade. Em estudo que avaliou 203 mulheres submetidas à histerectomia por patologias ginecológicas benignas em 24 e 48 horas de período pós-operatório, a intensidade da dor pré e pós-operatória foi mensurada pela Escala Verbal Numérica de 11 pontos. Cento e quarenta e duas pacientes (72%) foram submetidas à histerectomia abdominal, 34 (17,14%) à histerectomia vaginal, 13 (6,7%) à histerectomia laparoscópica e seis (3,1%) à histerectomia vaginal laparoscopicamente assistida. Um escore de dor ≥ 4 na EVN foi considerado pelos autores como moderado ou severo. Ao final do modelo de regressão logística aplicado, idade (OR: 0,90; IC 95%: 0,86-0,95), dor pré-operatória (OR: 2,50; IC 95% = 1,12-5,60) e catastrofização à dor (OR: 3,37; IC 95%:1,63-6,95) foram associadas à dor pós-operatória moderada ou severa (PINTO, 2012a). Os autores também publicaram resultados quatro meses após a cirurgia (186 pacientes). A metade das pacientes (93) ainda referia dor, e 48 delas (25,81%) referiam dor diária. Os fatores associados à dor crônica pós-operatória na regressão logística foram: idade, presença de dor pré-operatória por outras causas, histerectomia abdominal e ansiedade (PINTO, 2012b).

Outros fatores não diretamente relacionados à técnica cirúrgica podem contribuir para a intensidade da dor pós-operatória. Estudo incluiu 342 pacientes

divididos em dois grupos: dor pós-operatória não severa (200) e dor pós-operatória severa (142). O uso de analgésicos prévio à cirurgia foi um fator independente associado à dor severa pós-operatória (OR: 1,91; IC 95%:1,15-3,18) (AUBRUN, 2008). Estudo realizado em Porto Alegre incluiu 346 pacientes submetidas a cirurgias abdominais. A intensidade da dor foi mensurada pela Escala Visual Analógica de 0-100 e dor moderada ou severa foi considerada a dor > 30 na EVA. Os pacientes clinicamente mais graves ASA III (OR: 1,99; IC 95%: 1,30-3,03), mais jovens (OR: 4,72; IC 95%: 2,69-8,32), com dor pré-operatória (OR: 1,75; IC 95%: 1,03-2,98), portadores de ansiedade (OR: 1,74; IC 95%: 1,12-3,36) ou depressão (OR: 2,00; IC 95%: 1,03-3,87) tiveram mais chance de apresentar dor moderada ou severa no período pós-operatório. Nesse estudo, cirurgia para câncer foi considerada um fator protetor (OR: 0,39; IC 95%: 0,20-0,77) (CAUMO, 2002).

Estudos randomizados comparando cirurgias oncológicas não ginecológicas laparoscópicas e abdominais também demonstraram menores escores de dor para as cirurgias laparoscópicas (KALTOFT, 2011; CHUNG, 2007). Dezoito pacientes portadores de carcinoma de sigmoide foram randomizados para serem submetidos à sigmoidectomia laparoscópica (10) ou à sigmoidectomia aberta (8) sem previsão de ostomia. O grupo submetido à laparoscopia referiu menor dor nas primeiras 24 horas e menor fadiga e menor necessidade de sono nos primeiros 30 dias após a cirurgia ($p = 0,033$ e $p = 0,036$, respectivamente). Nesse estudo, a equipe de enfermagem, os médicos que trataram os pacientes após a cirurgia e os pacientes foram cegados para a técnica cirúrgica empregada. Ambos os grupos receberam o cuidado perioperatório padrão, foram quantificadas as horas despendidas no cuidado de enfermagem dos dois grupos e não houve diferença estatisticamente significativa entre eles. A dor foi mensurada diariamente durante a internação pela Escala Visual Analógica de 11 pontos (KALTOFT, 2011). Estudo randomizou 81 pacientes com diagnóstico de carcinoma de cólon ascendente não metastático. Quarenta e um pacientes foram submetidos à colectomia laparoscópica, e 40 pacientes foram submetidos à colectomia aberta. A intensidade da dor foi mensurada pela Escala Visual Analógica de 11 pontos. Os pacientes submetidos à abordagem laparoscópica apresentaram menores escores de dor (2,5 *vs.* 6; $p < 0,001$) (CHUNG, 2007). Outro estudo randomizou 164 pacientes portadores de carcinoma gástrico inicial. Oitenta e dois pacientes foram randomizados para serem submetidos à gastrectomia laparoscópica distal, e 82 pacientes foram submetidos à gastrectomia distal aberta.

Os desfechos de qualidade de vida foram avaliados pelo *European Organization for Research and Treatment of Cancer – Quality of Life Questionaire* (EORTC-QLQ). O grupo operado por laparoscopia recebeu uma quantidade significativamente menor de analgésicos no período pós-operatório; na comparação dos escores da escala utilizada, o grupo operado por laparoscopia apresentou menos dor do que o grupo operado pela via abdominal (KIM, 2008).

Estudo randomizado comparou 19 pacientes que foram submetidas à miomectomia laparoscópica e 21 pacientes que foram submetidas à miomectomia abdominal. Os escores de dor foram mensurados pela Escala Visual Analógica de 10 pontos, em 24, 48 e 72 horas de período pós-operatório. Não houve diferença estatisticamente significativa nos escores de dor em 24 horas após a cirurgia (3,5 ± 1,8 *vs.* 4,4 ± 1,6). O grupo submetido à miomectomia laparoscópica apresentou escores de dor significativamente menores do que o grupo submetido à miomectomia abdominal em 48 horas (2.1 ± 1.5 vs. 4.0 ± 2.3; p > 0.01) e em 72 horas (1.1 ± 3.7; p > 0.01) após a cirurgia (HOLZER, 2006). Meta-análise da Biblioteca Cochrane incluiu três estudos comparando laparoscopia (110 pacientes) e laparotomia (108 pacientes) para a exérese de tumores benignos ovarianos. A chance de estar sem dor em 24-48 horas foi significativamente maior no grupo laparoscópico (OR: 7,35; IC 95%: 4,3-12,56) (MEDEIROS, 2008).

Estudo retrospectivo comparou 20 pacientes submetidas à histerectomia radical vaginal e linfadenectomia laparoscópica e 22 pacientes submetidas à histerectomia radical vaginal e linfadenectomia extraperitoneal. Não houve diferença estatisticamente significativa nos escores de dor pós-operatórios, que foram avaliados pela EVA de 10 pontos (LARCIPRETE, 2006).

Alguns autores publicaram resultados comparando a histerectomia laparoscópica (tipo Piver I) com a histerectomia abdominal para o tratamento do carcinoma de endométrio. Estudo randomizou 535 pacientes submetidas à laparoscopia e 267 pacientes submetidas à laparotomia. A dor pós-operatória foi avaliada por dois itens do *Brief Pain Inventory* para avaliar os extremos de intensidade de dor. A intensidade da dor foi significativamente menor para o grupo submetido à laparoscopia em uma semana (p = 0,004) e três semanas (p = 0,013) após a cirurgia (KORNBLITH, 2009). Outro estudo multicêntrico norueguês randomizou 187 pacientes para serem submetidas à histerectomia laparoscópica e 96 pacientes para serem submetidas à laparotomia. As pacientes do grupo

submetido à laparoscopia necessitaram menor quantidade de analgésicos no período pós-operatório ($p < 0,0001$). Entretanto não houve diferença entre os grupos na intensidade da dor, avaliada pela EVA, embora essa escala só tenha sido aplicada seis semanas após a cirurgia (MOURITS, 2010). Outro estudo randomizou 42 pacientes para serem submetidas à laparoscopia e 42 pacientes para serem submetidas à laparotomia. Não houve diferença nos escores de dor medidos pela EVA nas primeiras 48 horas após a cirurgia, mas a quantidade de analgésicos utilizada pelo grupo laparoscópico foi menor, e os escores da EVA foram significativamente menores no grupo laparoscópico no dia da alta hospitalar ($p < 0,05$) (ZULLO, 2005).

Ensaio clínico randomizado (NAIK, 2010) comparou a histerectomia radical vaginal laparoscopicamente assistida (HRVLA, com oito pacientes) e a histerectomia radical abdominal (HRA, com sete pacientes) para o tratamento do carcinoma de colo uterino IB menores de 2 cm. Nesse estudo não houve avaliação direta da intensidade da dor, mas o consumo de morfina nas primeiras 36 horas de período pós-operatório foi significativamente menor no grupo submetido à laparoscopia HRVLA, que teve consumo médio de 30 ml (20-46), contra 53 ml (43-210) na HRA.

Não foram localizados na literatura ensaios clínicos randomizados comparando a histerectomia radical laparoscópica e histerectomia radical aberta para o tratamento do carcinoma de colo uterino inicial. Em 2008, foi publicado um protocolo internacional delineado para incluir 740 pacientes a fim de avaliar a factibilidade, as complicações, a qualidade de via e a sobrevida de pacientes randomizadas para realizar histerectomia radical laparoscópica/robótica ou histerectomia radical abdominal. As técnicas serão consideradas equivalentes se a diferença nas taxas de sobrevida não exceder 7% em quatro anos de seguimento (OBERMAIR, 2008).

O presente estudo foi planejado para comparar a dor pós-operatória e a factibilidade da histerectomia radical laparoscópica no contexto assistencial usual durante a introdução da técnica laparoscópica no Serviço de Ginecologia do Hospital Nossa Senhora da Conceição. Nós incluímos pacientes de 1999 a 2004. Nossa hipótese é que as pacientes submetidas à histerectomia radical laparoscópica apresentarão menor dor pós-operatória com taxas de complicações e sobrevida equivalentes. Nossos objetivos são comparar dor pós-operatória, complicações sobrevida da HRL e da HRA.

2 JUSTIFICATIVA

A histerectomia radical abdominal é um dos tratamentos preconizados pela Federação Internacional de Ginecologia e Obstetrícia (FIGO) para o carcinoma de colo uterino inicial. Estudos retrospectivos já demonstraram a factibilidade e a segurança da histerectomia radical laparoscópica. Além disso, ensaios clínicos randomizados para o tratamento de patologias ginecológicas benignas, comparando a abordagem laparoscópica à abordagem abdominal, demonstraram que a abordagem laparoscópica apresenta menor dor pós-operatória e menor tempo de internação. Estudos retrospectivos comparando a histerectomia radical laparoscópica e a abdominal descreveram uma menor taxa de complicações para a via laparoscópica. Se as taxas de sobrevida em cinco anos forem comparáveis entre as duas técnicas e a histerectomia radical laparoscópica apresentar melhores desfechos de curto prazo, a opção preferencial pela via laparoscópica estaria justificada.

3 OBJETIVOS

3.1 OBJETIVO PRINCIPAL

Comparar a dor pós-operatória entre as pacientes que foram submetidas à histerectomia radical laparoscópica com linfadenectomia e as que foram submetidas à histerectomia radical abdominal com linfadenectomia.

3.2 OBJETIVOS SECUNDÁRIOS

1) Comparar tempo cirúrgico e características histopatológicas entre as pacientes que foram submetidas à histerectomia radical laparoscópica com linfadenectomia e as que foram submetidas à histerectomia radical abdominal com linfadenectomia.
2) Comparar as taxas de complicações perioperatórias entre os grupos.
3) Comparar a sobrevida e a sobrevida livre de doença em cinco anos entre os grupos.
4) Descrever a experiência cirúrgica da equipe com histerectomia radical laparoscópica.

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5 ARTIGOS CIENTÍFICOS

5.1 ARTIGO I – "VIDEOLAPAROSCOPIC RADICAL HYSTERECTOMY APPROACH: A TEN-YEAR EXPERIENCE"[1]

SCIENTIFIC PAPER

Videolaparoscopic Radical Hysterectomy Approach: a Ten-Year Experience

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ABSTRACT

Background: Because of the advancements in surgical techniques and laparoscopic instruments, total laparoscopic radical hysterectomy can now be performed for the treatment of uterine cervical carcinoma. We assessed the feasibility, complications, and survival rates of patients who underwent total laparoscopic radical hysterectomy with pelvic lymphadenectomy.

Methods: We retrospectively collected data from the medical charts of 29 patients who had undergone surgery between 1998 and 2008. The following data were assessed: age, staging, histological type, number of lymph nodes retrieved, parametrial measures, operative time, length of hospital stay, surgical complications, and disease-free time.

Results: The mean patient age was 37.07±10.45 years. Forty percent of the patients had previously undergone abdominal or pelvic surgeries. Mean operative time was 228.96±60.41 minutes, and mean retrieved lymph nodes was 16.9±8.12. All patients had free margins. No conversions to laparotomy were necessary. Median time until hospital dismissal was 6,5 days (range 3–38 days). Four patients had intraoperative complications: 2 lacerations of the rectum, 1 laceration of the bladder, and 1 lesion of the ureter. Three patients developed bladder or ureteral fistulas postoperatively that were successfully corrected surgically.

Conclusion: Laparoscopic radical hysterectomy is feasible and has acceptable complications. The radicalism of the surgery must be considered, bearing in mind the parametrial measures and the number of lymph nodes retrieved.

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Key Words: Laparoscopy, Radical hysterectomy, Cervical cancer, Complication, survival.

INTRODUCTION

Radical hysterectomy for the treatment of uterine cervical carcinoma was first described in 1895. The initial mortality rate for this surgery was high, approximately 19%.[1] In 1955, Meigs[2] published a report on a series of 100 patients who underwent surgery. All of them survived; thus, Meigs had introduced pelvic lymphadenectomy.

With good cure rates for the treatment of uterine cervical carcinoma, various strategies are being developed to reduce the morbidity associated with traditional treatments without compromising survival rates.[3] Videolaparoscopic surgical techniques have begun to play a significant role in the treatment of uterine cervical carcinoma.

The first description of laparoscopic radical hysterectomy (LRH) was by Nezhat et al[4] in 1992 when they described a procedure performed on a patient with uterine cervix 1A2. This procedure featured a 7-hour operative time and retrieval of 14 pelvic lymph nodes. However, only recently have authors started to publish their experiences with this surgical technique,[5–10] probably due to advancements in surgical techniques and materials. Comparative studies recently detected a shorter hospital stay and less blood loss[10,11] but longer operative times with laparoscopic access.[10–12]

In 1998, we started to use this surgical approach in our service, and presently it is the technique of choice for treating patients with initial uterine cervical carcinoma. This study describes the adaptation of the laparotomic technique proposed by the team and the experience with this technique, including 29 nonconsecutive patients operated on between 1998 and 2008.

METHODS

Data collection from medical charts was authorized by the Research Ethics Committee of Nossa Senhora da Conceição Hospital. All patients who underwent radical laparo-

[1] Artigo descrevendo a experiência da equipe na realização da histerectomia radical laparoscópica, publicado na *Journal of the Society of Laparoendoscopic Surgeons* em 2009.

scopic hysterectomy with pelvic lymphadenectomy between 1998 and 2008 were retrospectively registered, and patients with primary uterine cervical carcinoma between stages IA2 and IIA were included. For these patients, a radical hysterectomy type III was proposed.[13] Patients for whom the procedure was suspended intraoperatively due to tumor unresectability were excluded. All patients had the same principal surgeon (Dr Limberger) and signed the free, informed consent about the surgical technique. Previous surgeries were not considered adverse conditions for the performance of a laparoscopic surgery.

The following data were collected: age, staging, operative time, intraoperative complications, need for blood transfusion, hospital stay, histological type, number of lymph nodes retrieved, parametrial and vaginal cuff measures, postoperative complications, and follow-up time. Staging was performed clinically as previewed by FIGO.[14] The blood loss estimate was assessed by the clinical need for a blood transfusion according to the anesthetist. Postoperative complications were divided into early (up to 30 days postoperatively) and late. Patients were dismissed with intermittent vesical catheterization, prophylaxis antibiotics, and suspension of vesical catheterization. A urinary residue <100 mL was considered sufficient to suspend catheterization. The parametrial and vaginal cuff were measured in their larger extension postoperatively through insertion in the uterine cervix by one of the team members or by the pathologist who examined the specimen.

Surgical Technique

Radical Hysterectomy

First, the upper members are fixed along the body. Vesical catheterization is then performed with a #18 catheter, and a uterine manipulator with chrome-plated tubing is put in place. This is the appliance we consider the most appropriate, because it allows full uterine and vaginal manipulation without intercepting the approach of pararectal and paravesical spaces or the rectum and parametrium at all its points. Insufflation using a Veress needle and supraumbilical puncture with a 10-mm trocar for a 30° optical introduction is performed. Insufflation begins with 1 L/min until the introduction of 2 Ide CO_2 into the cavity, when we increase to the maximum insufflation available with the device. We work with pressures that vary from 15 mm Hg to 18 mm Hg, according to patient tolerance. Then we perform a revision of the peritoneal cavity followed by performance of 3 other 5-mm suprapubic punctures. Sealing and sectioning of the vessels of the infundibular pelvic ligament follows, a section of the round ligament is taken, an opening is made in the large ligament along the superior vesical artery, and a paravesical space up to the muscular planes is instituted. The pararectal space is over the ureter, which is identified posteriorly. This space is opened to liberate the rectum, and the ureter posteriorly and the parametrium anteriorly, until the pararectal space communicates with the paravesical space. Then a section of the uterine vessels in confluence with the internal iliac vein is taken, as is tissue from the parametrium close to the bone wall. Dissection of the vesicouterine peritoneum with rhomboid detachment of the bladder is accomplished, and gauze is introduced by using the optical trocar and opening the vagina. Cranial impulsion of the uterus and separation of the bladder from the vaginal wall is performed to the point of insertion of ureters. The ureter is detunnelized, removing it from the total extension of the parametrium until it penetrates the bladder wall, freeing it completely. Dissection of the paracolpium is performed to completely free the parametrium and the lateral wall of the vagina. This is done contralaterally. Dissection and liberation of the rectum from the posterior vaginal wall is performed to resect the entire uterosacral ligaments. Once the pneumoperitoneum is reversed, the uterine manipulator is removed, and extracting tweezers are used to preserve the pneumoperitoneum, which is fixed to the lateral opening and the uterine cervix. Circumferential sectioning of the vagina is then performed. The uterus is retrieved through the vagina, and physiological serum is applied by using a gloved finger to conduct vaginal tamponing to remake the pneumoperitoneum.

Pelvic Lymphadenectomy

Dissection starts in the external iliac artery then moves externally to the anterior fascia of the genitocrural nerve, continuing inferiorly to the Cloquet lymph node that is located internally by the hypogastric vessel, superior to the internal circumflex iliac vein and the internal inguinal orifice. Dissection continues over the Cooper ligament, moving down the internal wall of the iliac vein. Then the lymphatic ducts internal to the nerve and the obturating vessels are dissected close to the bifurcation of the iliac veins. Isolated dissection of the group of lymph nodes under the ureter and close to the common iliac veins is performed. These lymph nodes are maintained in gloved fingers previously marked to identify right and left. Performance is contralateral. The material is retrieved through the vagina. The cupola is sutured laparoscopically. Closed aspiration drainage is maintained until lymph collection is <100 mL in 24 hours.

Data were registered and statistical analysis was performed using version 6.04 b of Epi-Info software. Normal distribution variables are described with mean and standard deviation. Non-normal distribution variables are described using medians and percentiles.

RESULTS

From December 1998 to March 2008, 29 patients in stages IA2 and IB underwent videolaparoscopic radical hysterectomy and pelvic lymphadenectomy with the technique described above. No surgery was converted to laparotomy, and no patient experienced anesthetic complications. The mean patient age was 37.07±10.45 years, and the parity median was 2 children. Forty percent reported abdominal surgery or previous pelvic surgeries, predominantly cesarean deliveries.

Mean operative time was 228.96±60.41minutes, with a minimum of 150 minutes and a maximum of 420 minutes. Three patients needed intraoperative blood transfusions. Median time until discharge was 6.5 days. Histological types included epidermoid carcinoma (69%), adenocarcinoma (24.1%), and adenosquamous carcinoma (6.9%), with mean retrieval of 16.9±8.12 lymph nodes with a minimum of 7 and a maximum of 37 lymph nodes, 3 of which were positive lymph nodes. All surgical specimens had free margins. Parametrial measurements were taken for 23 patients, and vaginal cuff measurements were taken for 27 patients. The right parametrium measured 5.69±2.58 cm, and the left parametrium measured 5.64±2.72 cm. The median vaginal length was 2.7 cm (p 25%, 1.7; p 75%, 3.5).

Four patients had intraoperative complications. One patient had an accidental bladder lesion in the dissection of the anterior portion of the vagina, which was detected during surgery. A laparoscopic repair was performed. Another patient had a distal rectal lesion detected intraoperatively and corrected through the vaginal approach. The third patient had an accidental ureteral lesion detected intraoperatively and a ureter re-implantation was done laparoscopically with the placement of a JJ catheter. These patients improved with complete recuperation of function without major recurrences. The last patient had a rectal lesion detected on the first postoperative day, and an open loop colostomy in the descending colon was performed with an exhaustive flushing of the cavity. This patient developed sepsis, deep venous thrombosis, and was further required to undergo a vesicovaginal fistula correction during a subsequent hospitalization. This patient was disease-free for 4 years and fitted with a colostomy pouch. The median hospital stay was 6.5 days with a minimum of 3 and a maximum of 38 days.

Eight patients had early postoperative complications: 3 had cystitis and received adequate antibiotic therapy; 2 had seroma; and 2 developed abdominal infection. All received adequate management. One patient developed a ureteral fistula on the 14th day postoperatively, which was initially unsuccessfully managed with a JJ catheter. She later successfully underwent a correction of the fistula 30 days after surgery. One patient developed a fistula on the second day postoperatively, which was corrected surgically but relapsed on the 15th day postoperatively. Four months after surgery, a left renal exclusion was diagnosed and a nephrostomy performed. Another surgical correction of the fistula was made 10 months after the LRH. Fifteen months after LRH, a left nephrectomy occurred due to pyelonephritis and a functional exclusion of the left kidney. This patient did not have new complications and has been disease free for 9 years.

Thirteen patients had late complications, 3 of which have already been mentioned. Six patients had cystitis. One patient developed a seroma with expectant conduct. Two patients had bladder insensitivity without urinary retention. One patient had a left ureteral fistula 37 days postoperatively, which was corrected successfully.

Follow-up data are available for 28 patients. Median follow-up time was 20.12 months with a minimum of 23 days and a maximum of 102.97 months. Nineteen patients (67.9%) were disease-free on the last consultation, 3 patients had controlled disease after relapse, and 6 patients died. One patient died due to primary breast cancer and the second due to primary bladder cancer, both without evidence of cervical carcinoma relapse. The 4 remaining patients died due to relapse or tumor metastasis. None of the deaths was due to surgical complications.

DISCUSSION

Feasibility and safety of laparoscopic radical hysterectomy has already been demonstrated in previous studies.[5–7] As of today, few are comparative studies, and we could not find any randomized prospective studies in the literature comparing videolaparoscopic and open techniques. Some controlled studies can be seen in **Table 1**, and comparative studies can be seen in **Table 2**.

In our series of cases, it was not necessary to convert to laparotomy, and only one patient needed a new intervention. Operative time and surgical complications[5–7] were similar to those described in other articles.[5–7,9] In the

Table 1.
Laparoscopic Radical Hysterectomy Without Laparotomic Control Group

Author	N	Operative Time (min)	Lymph Nodes	Follow-up (months)	Survival Rate
Spirtos[5] 2002	78	205 (150–430)	23.8	66.8	89.7%
Obermair[7] 2003	39	210 (90–410)		36.5	87.4%
Gil-Moreno[8] 2005	27	285 (CI95%:273.1–296.5)	19 (CI: 17.02–21.12)	32	100%
Ramirez[6] 2006	20	332.5 (275–442)	13 (9–26)	8	100%
Lee[9] 2007	76	228.9 (121–352) 171.8 (65–267)	21.1 (7–41) 15.9 (4–52)	12–60	1 relapse with death

Table 2.
Radical Laparoscopic Surgeries and Pelvic Lymphadenectomy Compared With Abdominal Radical Hysterectomy

Author	N*	Staging	Operative Time (min)*	Lymph Nodes*	Follow-up	Survival Rate*	Controls
Frumovitz[11] 2007	HRL 35 HRA 55		HRL 344 HRA 304†	HRL 14 HRA 19	-	-	History
Zakashanskyy[10] 2007	HRL 30 HRA 30		HRL 318.5 (200–464) HRA: 242.5 (75–353)†	HRL 31 (10–61) HRA 21.8 (8–42)†	-	-	Controls obtained by computer
Li 2007[12]	HRL 90 HRA 35	IB-IIA	HRL 262.99 ± 67.6 HRA 217 ± 71.56†	HRL 21.28 ± 1.39 HRA 18.77 ± 9.47	26 Months	HRL 90% HRA 86.25%	-

*HRL = laparoscopic hysterectomy; HRA = abdominal hysterectomy.

† $P<0.05$.

Spirtos series[5] (78 patients), a patient needed a blood transfusion, and 3 bladder lesions were found. Two patients needed laparotomies to control bleeding, and there was a vesicovaginal fistula. In the series published by Ramirez et al,[6] with 20 patients, one needed a blood transfusion, one had a bladder lesion, and one developed pneumomediastinum. One patient had a pulmonary embolism, one had late evisceration postoperatively, and one developed a lymph cyst. In Obermair's[7] study with 55 patients, 39 with uterine cervical carcinoma, 3 procedures were converted to laparotomy due to uncontrollable intraoperative bleeding. Two patients had pulmonary embolisms, one of whom died. One vesicovaginal and one rectovaginal fistula have occurred. In Lee's[9] case-control study, the performance of videolaparoscopic radical hysterectomy with bipolar pulse energy and conventional bipolar electro surgery in 76 patients were registered as a rectal laceration and a vaginal fistula.

Few studies have reported the survival time of patients. In the series published by Spirtos,[5] 3 patients had microscopically positive or short margins. The recurrence rate was 5.1% in 3 years. In another study with follow-up times of between 12 and 60 months, one death was observed due to tumor recurrence.[9] In Obermair's[7] series with a follow-up time of 36.5 months, 3 patients developed metastatic disease. In our study, the percentage of disease-free patients was 69% with a median follow-up time of 20.9 months. This survival time could be related to the fact that we included patients in stage IB2 whose survival rate is inferior.[15] The median tumor size in our study was 1.9 cm.

One of the concerns in oncological surgery is the radicalism of the resection. In our study, the number of lymph nodes removed was similar to that in some laparoscopic radical hysterectomy studies.[5,6,8] The feasibility of videolaparoscopic lymphadenectomy has already been described in comparative studies.[16] To assess histopathologic variables of patients who underwent radical laparoscopic hysterectomy[10] compared with historic controls,[10] a recent study analyzed surgical specimens obtained with both techniques. The measurements of surgical specimens were compared, respectively: right parametrium 3.8 cm (range, 2.3 to 6.5) and 3.4 cm (range, 1.7 to 7), $P=0.59$; left parametrium 3.6 cm (range, 2 to 6) and 3.5 cm (range, 1.5 to 6.5), $P=0.82$. The authors con-

cluded that extension of the surgical dissection seemed to be similar between the 2 techniques.[15] In our series, parametrial measures were similar to those described in this study

CONCLUSION

Surgical procedures were performed within an adequate time and observed complications seem to be acceptable and similar to those described in other studies. The radicalism of our surgical technique seems to be acceptable and similar to that described in other studies. The radicalism of a particular operation is contemplated, bearing in mind parametrial measures and the number of lymph nodes retrieved. Comparative randomized prospective studies are necessary to answer the questions regarding patient survival rates.

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5.2 ARTIGO II – LAPAROSCOPIC VERSUS ABDOMINAL RADICAL HYSTERECTOMY WITH PELVIC LYMPHADENECTOMY IN PATIENTS WITH EARLY CERVICAL CANCER – A RANDOMIZED CLINICAL TRIAL[2]

Brazilian Journal of Videoendoscopic Surgery

Original Article

Laparoscopic *versus* Abdominal Radical Hysterectomy with Pelvic Lymphadenectomy in Patients with Early Cervical Cancer: A Randomized Clinical Trial

Histerectomia Radical Laparoscópica *versus* Abdominal com Linfadenectomia Pélvica em Pacientes com Câncer de Colo Inicial: um Estudo Clínico Randomizado

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ABSTRACT

Background: Radical hysterectomy with pelvic lymphadenectomy is one of the FIGO (International Federation of Gynecology and Obstetrics) recommended treatments for early cervical cancer. The laparoscopic approach has been described in the literature as feasible and safe. The objective of this study was to compare laparoscopic radical hysterectomy and open radical hysterectomy in a single center using a randomized clinical trial. There are no completed randomized controlled trials comparing laparoscopic radical hysterectomy and abdominal radical hysterectomy, although one trial is ongoing. **Methods/Design:** 30 stage IA2 patients with lymphatic vascular space invasion or stage IB cervical cancer patients were enrolled. Postoperative pain intensity was the primary endpoint; the sample size necessary was calculated to be 30 patients. Pain intensity was measured using a 10-point numeric rating scale. Both surgical techniques were executed by the same surgical team. Secondary outcome measures included intraoperative and postoperative complications, histopathologic findings, and overall and disease-free survival during a 5-year follow-up period. Patients were randomized using a random number table. IRB approval was obtained in 1999, and patients were enrolled between late 1999 and early 2004. This article described the study protocol in detail. The data analysis is currently being performed and will be reported in a subsequent article. **Trial Registration: NCT01258413.**

Key words: Cervical cancer. Laparoscopic. radical hysterectomy.

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INTRODUCTION

Cervical cancer is the second most common cancer among women worldwide, and 83% of cases occur in developing countries.[1] In Brazil, the estimated annual incidence is about 19 cases per 100,000 women.[2] The cure rate for radical hysterectomy with pelvic lymphadenectomy is up to 80% in stages IB e IIA patients with a tumor size of less than 4 cm, and is around 70% in patients whose tumors exceed 4 cm.[3, 4] Tumor size, lymphovascular space invasion and positive nodes all decrease disease-free survival[4, 5] and require adjuvant pelvic radiotherapy.[5, 6] Radiotherapy and surgery, when compared in randomized clinical trials, have been shown to have similar survival rates.[3, 7]

The reported benefits of a laparoscopic versus an open approach for benign gynecological diseases include decreased postoperative pain and a shorter hospital stay.[8, 9] Several randomized studies have reported an increased operative time.[9, 10]

Various studies have reported the feasibility and safety of a laparoscopic radical hysterectomy.[11-13] Non-randomized comparative studies have shown

Abbreviations: *laparoscopic radical hysterectomy (LRH); abdominal laparoscopic radical hysterectomy (ARH); numeric rating scale (NRS); FIGO (International Federation of Gynecologic and Obstetrics)*

[2] Artigo descrevendo o protocolo da pesquisa publicado na *Brazilian Journal of Videoendoscopic Surgery* no terceiro trimestre de 2011.

an increased operative time,[14-16] a shorter hospital stay,[14, 15] and fewer postoperative infections [14] when laparoscopic radical hysterectomy was compared with the open approach. Preliminary data suggest an equivalent survival between the two techniques.[16, 17]

No randomized trials are available that compare laparoscopic radical hysterectomy with an abdominal laparoscopic hysterectomy for treating early stage cervical cancer. A randomized, international protocol was elaborated; it calls for the enrollment of 740 patients to evaluate the feasibility, complications, quality of life, and survival in early stage cervical cancer patients assigned to either abdominal or laparoscopic/robotic radical hysterectomy. Equivalence will be declared if the difference in the disease-free survival between the two trial arms does not exceed 7% at four years.[18] The protocol was designed to compare postoperative pain, postoperative complications, and survival rates after laparoscopic radical hysterectomy (LRH) versus abdominal radical hysterectomy (ARH) for early stage cervical cancer in usual care settings. This analysis considered patients operated from 1999 to 2004, years when the laparoscopic technique was being introduced in Brazil.

Our hypothesis was that a laparoscopic radical hysterectomy will result in decreased postoperative pain compared to an abdominal radical hysterectomy, but will have similar postoperative complications and survival rates.

MATERIAL AND METHODS

This article details the study protocol as a single center randomized controlled trial comparing laparoscopic radical hysterectomy (LRH) and abdominal laparoscopic radical hysterectomy (ARH). Eligible patients were randomized to undergo either LRH or ARH

Ethical considerations

The Ethics Committee of Grupo Hospitalar Conceição approved the study protocol in 1999. This protocol was registered at ClinicalTrials.gov

Primary endpoint

The primary outcome is postoperative pain as measured by a 10-point numeric rating scale (NRS) during the postoperative period. Pain was assessed every six hours by nursing staff during a patient's usual postoperative care. The nursing staff was not aware of the study objective.

Secondary endpoints

1. Operative variables included the following: operative time (minutes), injuries to the ureter, bladder, bowel or vessels requiring blood transfusion, and anesthesia complications.

2. Surgical and pathologic variables included the following: histological type, surgical margins, lymph node status and lymph node number, all assessed by pathologists with expertise in gynecologic oncology. In addition, parametrial and vaginal cuff width (centimeters) was assessed by the primary surgeon in the operating room, before tissue processing.

3. Early (< 30 days) postoperative events and findings during the hospital stay including: duration in days of the hospitalization, complications, need for extra analgesic drugs, and all clinical and surgical events during this period.

4. Clinical or surgical findings that could be attributable to the treatment or the disease through five years of follow-up.

5. Date and anatomic site of the first recurrence or metastasis within the first five years of follow-up.

6. Overall survival and disease-free survival at five years of follow-up

Eligibility Criteria

Inclusion Criteria: women at least 18 years of age referred to our service with histologically confirmed primary squamous, adenocarcinoma or adenosquamous cervical cancer diagnosed by biopsy or cervical conization and clinically staged according to the International Federation of Gynecologic and Obstetrics (FIGO) classification as IA2 with lymph vascular invasion, IB, or IIA [5].

Exclusion Criteria: patients with clinically advanced disease (stages IIB-IV), previous pelvic or abdominal radiotherapy, current pregnancy, or clinical diseases that would preclude one or both surgical approaches.

Surgical team

All surgeries were performed by the same team. The first surgeon (LFC) performed all surgeries and two other team members (RK and LSC) served as first or second assistants. The first surgeon had already performed more than one hundred abdomin

radical hysterectomies before performing laparoscopic radical hysterectomies. [19]

STANDARDIZATION OF SURGICAL PROCEDURE

Before the beginning of the study, a surgeon with expertise in abdominal radical hysterectomies evaluated the digital records of other laparoscopic radical hysterectomies performed by the first surgeon. To assess the adequacy of the oncologic resection, the first surgeon measured the parametrial and vaginal tissue in the operative room before tissue processing.[20]

SURGICAL TECHNIQUES

Laparoscopic Radical Hysterectomy: A Foley catheter and a uterine manipulator with chrome plated tubing were placed under sterile conditions. This manipulator allowed for full uterine and vaginal manipulation without interfering with the approach of the pararectal and paravesical spaces, the rectum or parametrial tissue. Supraumbilical insertion of a Veres needle was employed for insufflation, and a 10-mm trocar was placed for a 30 degree laparoscope. The intra-abdominal pressure was maintained between 15 and 18 mmHg. The abdominal cavity was then inspected. Three additional 5mm trocars were inserted next. Then the vessels of the infundibulopelvic ligament were coagulated and cut. The round ligament was transected, and the broad ligament was opened along the superior vesical artery, thereby opening the paravesical space to the muscular plane. The ureter was posteriorly identified, after which the pararectal space was opened and the rectum was freed, keeping the ureter posterior and the parametrium anterior, until it communicated with the paravesical space. The uterine vessels were transected until they were confluent with the internal iliac vein. The parametrial tissue close to the pelvic bone was then transected. The ureter was unroofed to the point of its insertion into the bladder, freeing it completely. A paracolpium dissection was performed to free the parametrium and lateral vaginal wall, and was repeated on the contralateral side. An incision of the rectal peritoneum was made to open the rectovaginal space. Dissection of the uterosacral ligaments was performed as close to the pelvic wall as possible. Blunt dissection of the bladder was performed with gauze, after dissection of the vesicouterine fold. The vagina was circumferentially transected, and the specimen was removed. The pneumoperitoneum was maintained using latex glove fingers filled with saline.

Laparoscopic pelvic lymphadenectomy: First, the right and left pelvic lymph nodes were dissected from the common external iliac artery to the circumflex iliac vein, and the tissue behind and between the iliac vessels was removed. The dissection started cephallically, with removal of the lymph nodes from the external iliac artery along the genitofemoral nerve and inferiorly/externally down to the level of the circumflex iliac vein. The Cloquet's node was identified, internal to the common iliac vein and superior to the circumflex internal iliac vein and the inguinal canal. The obturator lymph nodes were removed by dissecting over Cooper's ligament along the internal iliac vein lymph nodes and dissecting the lymph ducts internal to the obturator vessels and nerve, ending at the iliac bifurcation. An isolated dissection of a small group of lymph nodes was also performed, under the ureter and next to the common iliac vessels. These specimens were removed vaginally, protected in identified glove fingers. The vaginal cuff was sutured laparoscopically. Closed-suction drainage was placed until daily drainage fell below 100 ml.

Abdominal radical hysterectomy: ARH was performed according to the Piver III classification for a radical hysterectomy.[21]

Antibiotic prophylaxis: One hour before surgery, and after 2 hours during the procedure, cefalotin 1g IV was administered for prophylaxis.

Anesthesia and postoperative analgesia: the same team of anesthesiologists performed anesthesia following a defined protocol. Patients were premedicated with midazolam 15 mg orally one hour before surgery, and once in the operating room. IV access was established and standard monitoring (ECG, noninvasive blood pressure, oxygen saturation and capnography) was measured. General anesthesia was induced with fentanyl 3 ì/Kg and propofol 2 mg/Kg. Orotracheal intubation was facilitated with atracurium 0.5 mg/Kg, and the orotracheal tube was inserted. After intubation, the lungs were ventilated with 50% O_2, 50% N_2O and sevoflurane 2%. Fentanyl and propofol were controlled to maintain a systolic blood pressure within 10% of the basal systolic pressure. At the beginning of the lymphadenectomy, ketoprofen 100 mg and metoclopramide 10 mg were administrated IV. Before extubation, dipyrone 15 mg/Kg IV and

morphine 0.05 mg/kg SC were administered. Residual neuromuscular blockade was antagonised with neostigmine and atropine, if necessary.

Postoperative analgesia: First day: diclofenac 75 mg IM BID, dipyrone 15 mg/kg IV QID, and morphine 0.05 mg/kg mg SC every four hours. Second day: diclofenac 50 mg PO TID and morphine 3 mg SC every four hours (on demand). Third day: diclofenac 50 mg PO TID (on demand) and morphine 3 mg SC every four hours (on demand).

Adjuvant radiotherapy / chemotherapy

Histopathological findings were used to determine the need for adjuvant postoperative treatment, at the discretion of the responsible physician.

Postoperative follow-up

All patients were evaluated by the study team in the early postoperative period. Most patients were followed up exclusively by the study team. Long-term follow-up should be for five years by the study team or a personal physician. Personal physicians were contacted periodically to ascertain the patients' status. All serious complications were documented and managed by the study team.

Sample size calculation

The NRS score scale was considered the primary postoperative endpoint. We expected a 55% difference in pain scale intensity between groups. The sample size calculated using Epi Info version 6.04b software in a 1:1 sample, was 30 patients. To compensate loss from follow-up, we decided to include 30 patients.

Randomization

Patients were randomly assigned to the laparotomy or laparoscopy by a random number table of 180 five-digit numbers generated by an independent author (ATS) who did not participate in patient selection, surgery or follow-up. After informed consent was obtained and prior to surgery, random allocation of a number was determined by a telephone call by a person unaware of the study objectives; the authors that participated in patient screening (LFL e LSC) did not had access to the random number table. Patients randomly allocated to even numbers underwent LRH and those with odd numbers underwent ARH. On the day before surgery, the nursing staff was trained to use the VAS scale. The nursing staff was not aware of the study objectives.

Statistical analysis

Patients will be analyzed according to the treatment group they are assigned to. Differences between two treatment groups will be tested for statistical significance with a two-sided Student t-test and Mann Whitney test for continuous data. A Chi-Square test will be used for categorical data and a Fisher exact test will be used for categorical variables. Survival and disease-free survival will be estimated by a Kaplan-Meier curve. P values < 0.05 will be considered statistically significant.

DISCUSSION

This single-center trial was designed to compare the severity of postoperative pain amongst IA2 and IB cervical cancer patients who agreed to be randomized to receive LRH or ARH as usual care. NRS is considered an appropriate statistical test to detect modifications associated with treatment across different cultures and settings.[22] This scale has previously been validated at our hospital in a sample of oncology patients.[23] The validity of a scale cannot be determined directly, but its agreement with another known scale can be evaluated.[24]

Using pain as the primary outcome measure requires the use of a surrogate endpoint. Although overall survival and disease-free survival are the primaryclinical endpoint in oncology, aspects related to quality of life are relevant in surgical trials because the procedure itself impacts early postoperative quality of life, which can be significant.[25]

Competing interests

All authors read and approved the final manuscript and declare that they have no competing interests.

Authors' contributions

Each author has sufficiently participated in the work to take public responsibility for portions of its content. LFL, LSC ATS designed this randomized clinical trial. LFL, RK, LSC performed the standardization of the surgical procedure. LFL, RK and LSC were the surgical team. LFL managed all surgical and clinical complications. LSC and LFL wrote this manuscript. ATS and ANK made significant contributions to protocol validity, design and drafting and revising this manuscript.

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This protocol was designed to take place in usual care setting and no additional source of funding was sought.

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RESUMO

Revisão: A histerectomia radical com linfadenectomia pélvica é uma das recomendações da FIGO (Federação Internacional de Ginecologia e Obstetrícia) no tratamento do câncer cervical inicial. O acesso pela laparoscopia tem sido descrito na literatura como possível e seguro. O objetivo deste estudo foi o de comparar a histerectomia laparoscópica radical e a histerectomia radical aberta em um único centro utilizando um estudo clínico randomizado. Não existem estudos controlados randomizados já finalizados comparando histerectomia radical laparoscópica e histerectomia radical abdominal, contudo um estudo encontra-se em andamento. **Métodos/Desenho:** 30 pacientes em estágio IA2 com invasão do espaço linfático vascular ou estágio IB pacientes com câncer cervical fizeram parte do estudo. A intensidade da dor pós-operatória foi considerada a marcação primária; o tamanho da amostra necessária foi calculada em 30 pacientes. A intensidade da dor foi mensurada utilizando uma escala numérica de 10 pontos. Ambas as técnicas cirúrgicas foram executadas pela mesma equipe de cirurgiões. As medidas dos resultados secundários incluíram complicações intra-operatórias e pós-operatórias, achados histopatológicos, e a sobrevida livre da doença e geral no período de 5 anos de acompanhamento. Os pacientes foram randomizados utilizando-se uma tabela de números aleatórios. A aprovação pelo comitê de ética foi obtido em 1999, e os pacientes incluídos no período final de 1999 ao início de 2004. Este artigo descreve o estudo do protocolo em detalhes. A análise dos dados esta sendo atualmente realizada e será publicada posteriormente em um artigo. **Registro do estudo: NCT01258413.**

Palavras – chave: Câncer cervical, histerectomia radical laparoscópica

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5.3 ARTIGO III – POSTOPERATIVE PAIN AND PERIOPERATIVE OUTCOMES AFTER LAPAROSCOPIC RADICAL HYSTERECTOMY AND ABDOMINAL RADICAL HYSTERECTOMY IN PATIENTS WITH EARLY CERVICAL CANCER: A RANDOMISED CONTROLLED TRIAL[3]

Campos et al. *Trials* 2013, **14**:293
http://www.trialsjournal.com/content/14/1/293

TRIALS

RESEARCH Open Access

Postoperative pain and perioperative outcomes after laparoscopic radical hysterectomy and abdominal radical hysterectomy in patients with early cervical cancer: a randomised controlled trial

Luciana Silveira Campos[1,2*], Leo Francisco Limberger[1], Airton Tetelbom Stein[1,2,3] and Antonio Nocchi Kalil[2]

Abstract

Background: Non-randomised studies have suggested that the postoperative complications of (Campos LS, Limberger LF, Stein AT, Kalil AN) laparoscopic radical hysterectomy are similar to those in abdominal radical hysterectomy. However, no study evaluating postoperative pain comparing both techniques has been published thus far. Our objective was to compare pain intensity and other perioperative outcomes between laparoscopic radical hysterectomy (LRH) and abdominal radical hysterectomy (ARH) in early cervical cancer.

Methods: This single centre, randomised, controlled trial enrolled 30 cervical cancer patients who were clinically staged IA2 with lymph vascular invasion and IB according to the FIGO (International Federation of Gynaecology and Obstetrics) classification, and underwent LRH or ARH between late 1999 and early 2004. Postoperative pain, as measured by a 10-point numerical rate scale, was considered the primary endpoint. Postoperative pain was assessed every six hours during a patient's usual postoperative care. Perioperative outcomes were also registered. Both surgical techniques were executed by the same surgical team. Secondary outcomes included intraoperative and other postoperative surgicopathological factors and 5-year survival rates.

Results: IA2 patients with lymphatic vascular space invasion and IB cervical cancer patients were randomised to either the LRH group (16 patients) or the ARH group (14 patients). Four patients (25%) in the LRH group and 5 patients (36%) in the ARH group presented with transoperative or serious postoperative complications. All of the transoperative complications occurred in the LRH group. The relative risk of presenting with complications was 0.70; CI 95% (0.23–2.11); $P = 0.694$. LRH group mean pain score was significantly lower than ARH after 36 h of observation ($P = 0.044$; mean difference score: 1.42; 95% CI: 0.04–2.80). The survival results will be published elsewhere.

Conclusions: LRH provided lower pain scores after 36 h of observation in this series. The perioperative and serious postoperative complications ratios were comparable between the groups.

Trial Registration: NCT01258413

Keywords: Cervical cancer, Laparoscopy, Radical hysterectomy

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[3] Artigo com o desfecho principal e os desfechos de curto prazo publicado na revista *Trials* em setembro de 2013.

Background

Cervical cancer is the second most common cancer among women worldwide, and 83% of cases occur in developing countries [1]. In Brazil, the estimated annual incidence is approximately 19 cases per 100,000 women [2]. Radical hysterectomy with pelvic lymphadenectomy is a (FIGO) International Federation of Gynaecology and Obstetrics recommended treatment for early cervical cancer [3], traditionally performed using the abdominal approach [4].

The advantages of laparoscopic versus the open approach for benign gynaecological diseases reported in the literature include decreased postoperative pain and a shorter hospital stay [5,6]. Some randomised studies have reported an increased operative time [6,7].

Previous studies have shown the feasibility and safety of laparoscopic radical hysterectomy (LRH) [8-10], and non-randomised controlled studies have suggested that LRH has an increased operative time [11-13], a shorter hospital stay [11,12], and fewer postoperative infections [12] compared with the open approach. A histopathological comparison of LRH and abdominal radical hysterectomy (ARH) suggested that they have the same radicality [14]. Preliminary data suggested an equivalent survival rate for the two techniques [13,15].

No randomised trials are available that compare laparoscopic radical hysterectomy with abdominal laparoscopic hysterectomy for treating early cervical cancer. A randomised, prospective international protocol was performed with 740 patients enrolled to evaluate the feasibility, complications, quality of life, and survival in early cervical cancer patients assigned to either abdominal (ARH) or laparoscopic/robotic radical hysterectomies (LRH). Equivalence will be declared if the disease-free survival difference does not exceed 7% at four years [16].

Methods

The detailed eligibility criteria, recruitment details, endpoints, standardisation of surgical procedures, surgical techniques, sample size calculation and randomisation methods have been published elsewhere [17]. The surgeons that performed the procedures assessed patients in postoperative care during hospital stay and its complications; during the follow-up, the same surgeons evaluated and managed the recurrences. The nurses who took care of the patients and who measured pain as the 5th vital sign during hospital stay were also not blind. Parametrial extension, vaginal cuff, and uterosacral ligament sizes were measured by the leading surgeon in the operative room. Operative time was measured by the study team surgeons. Other surgicopathological factors were assessed by the attending pathologist after tissue processing.

Briefly, this is a single centre, randomised, controlled trial comparing the hysterectomy LRH and ARH procedures. Eligible patients were randomised in either the LRH or ARH groups. The primary endpoint was postoperative pain, as measured by a 10-point numerical rating scale (NRS) during the postoperative period. Pain was assessed every 6 h by the nursing staff during a patient's usual postoperative care; the nursing staff had been trained at the beginning of the study. One day pre-surgery, they were reminded to ask each patient to score her pain level from 0–10; the nursing staff was unaware of the study objective. The secondary outcomes were intraoperative and postoperative complications, histopathological characteristics, overall survival and disease-free survival; these outcomes were registered prospectively.

Inclusion criteria

The following inclusion criteria were applied: women ≥18 years who sought treatment for histologically confirmed primary squamous, adenocarcinoma, or adenosquamous cervical cancer that was diagnosed by biopsy or cervical conization and clinically staged according to the FIGO classification of IA2 with IB or II A lymph vascular invasion [3].

Exclusion criteria

The following exclusion criteria were applied: patients with clinically advanced disease (IIB-IV), previous pelvic or abdominal radiotherapy, pregnancy or clinical diseases that would preclude one or both surgical approaches (pulmonary obstructive disease poorly controlled or contraindicating prolonged Trendelenburg position, severe hip disease precluding the use of the dorsolithotomy position; inadequate bone marrow, renal, or hepatic function); obesity; previous abdominal or pelvic surgery and demographic factors were not considered exclusion criteria.

Each surgery was performed by the same team. The leading surgeon (LFC) performed all of the surgeries, and the other team members were first or second assistants (RK and LSC). The leading surgeon had performed more than one hundred abdominal radical hysterectomies before performing laparoscopic radical hysterectomies. Before the beginning of the study, a surgeon with expertise in abdominal radical hysterectomies standardised the surgical technique by evaluating the digital records of the laparoscopic radical hysterectomies that were performed by the first surgeon. To evaluate oncologic adequacy, the leading surgeon measured the parametrial and vaginal tissue in the operative room before processing the tissue [18].

Surgical techniques

Laparoscopic radical hysterectomy and laparoscopic pelvic lymphadenectomy

Both procedures were performed as previously described [8,9,19]; LRH involves placing a uterine manipulator

with chrome place tubing. Access to the abdominal cavity was obtained though insertion of Verres needle and insufflation before placement of a 10-mm trocar. Laparoscopic radical hysterectomy was performed according to Piver III classification for a radical hysterectomy [20]. The vaginal cuff was sutured laparoscopically. Close-suction drainage was placed until the daily drainage fell below 100 mL.

ARH was performed according to the Piver type III classification for a radical hysterectomy [20]. Access to the abdominal cavity was obtained through a vertical midline skin incision.

Anaesthesia and postoperative analgesia

The same team of anaesthesiologists performed anaesthesia following a defined protocol: midazolam 15 mg orally one hour before surgery, IV access and standard monitoring. General anaesthesia was induced with fentanyl 3 μg/kg and propofol 2 mg/kg. Orotracheal intubation was facilitated by atracurium 0.5 mg/kg. After intubation, the lungs were ventilated with 50% O_2, 50% N_2O, and 2% sevoflurane. At the beginning of the lymphadenectomy, ketoprofen 100 mg and metoclopramide 10 mg were administrated via IV. Before the extubation, dipyrone 15 mg/kg IV, and morphine 0.05 mg/kg SC were administered. Residual neuromuscular blockade was antagonised with neostigmine and atropine when necessary.

Postoperative analgesia: Day 1, diclofenac 75 mg IM BID, dipyrone (15 mg/kg) IV QID and morphine 0.05 mg/kg mg SC every four hours; Day 2, diclofenac 50 mg PO tid and morphine 3 mg SC every four hours (on demand); Day 3, diclofenac 50 mg PO on demand and morphine 3 mg SC every four hours (on demand).

Adjuvant radiotherapy/chemotherapy

At the discretion of the responsible physician, the histopathological findings were used to determine the need for adjuvant postoperative treatment.

Postoperative follow-up

All of the patients were evaluated by the study team in the early postoperative period. The long-term follow-up was a minimum of five years by the study team or the patients' assistant physician. Periodically, contact was made with the assistant physician by the surgeons of the study team to ascertain the patients' status. All serious complications were documented and managed by the study team.

Assessing perioperative complications

All of the transoperative and serious postoperative complications were noted. We analysed the proportion of patients presenting with perioperative complications in both groups.

Sample size calculation

The NRS scale was considered the primary postoperative endpoint. We expected a 55% difference in pain scale intensity between the groups. The sample size was calculated by Epi Info version 6.04b software in a 1:1 sample, and we obtained 30 patients.

Randomisation

The patients were randomly assigned to groups using a random number table of 180 five-digit numbers

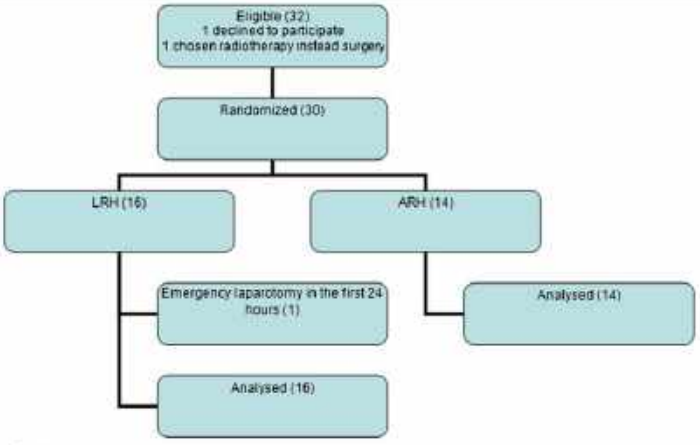

Figure 1 Study flowchart.

Table 1 Patient characteristics

Variables[1]	ARH (14)	LRH (16)
Age	39.64 ± 6.23	36.19 ± 9.78
Number of pregnancies	3.5 (3.0–4.0)	2.5 (1.5–3.5)*
Smoking	6 (43%)	5 (31%)
Previous conization	6 (43%)	8 (50%)
Previous abdominal or pelvic surgery	5 (36%)	7 (44%)

[1]Described as mean ± standard deviation or median (percentile 25–75), if quantitative. If categorical n (%).
*P <0.05.

generated by an independent author (ATS) who did not participate in patient selection, surgery or follow-up. After informed consent signing and prior to surgery, a random allocation number was determined with a telephone call.

Statistical analysis

Continuous variables with normal distribution were analysed using Student's *t*-test for independent samples and described by means and standard deviation, whereas those not consistent with normal distribution were analysed using the Mann-Whitney *U* test and described as medians and percentiles. The discrete variables were compared using Pearson's χ^2 test, and Fisher's exact test was used when any cell was <5. The pain scores and intergroups were analysed with an ANOVA for the repeated measures, and the Bonferroni correction was applied as necessary. Statistical significance was set at $P < 0.05$. The statistical software package SPSS (Statistical Package for the Social Sciences) version 18.0 was used for all data analysis.

Ethical considerations

The Ethics Committee of Grupo Hospitalar Conceição approved the study protocol in 1999. This protocol was registered at ClinicalTrials.gov. Written informed consent was obtained from all patients prior to enrolment.

Table 2 Surgicopathological factors

Variables	ARH (14)	LRH (16)
Squamous	12 (86%)	12 (75%)
Adenocarcinoma	2 (14%)	4 (25%)
LVSI[1]	6 (43%)	4 (25%)
Lymph nodes (number)	19.43 ± 6.35	19.5 ± 8.41
Right parametrial tissue[2]	4.14 ± 1.56	6.44 ± 2.59*
Left parametrial tissue[2]	4.01 ± 1.42	6.33 ± 2.2*
Right uterosacral ligament	2.34 ± 0.91	2.78 ± 1.1
Left uterosacral ligament	2.26 ± 0.97	2.67 ± 1.1
Vaginal cuff	2.41 ± 1.18	3.17 ± 1.28
Operative time	240.36 ± 26.85	264.38 ± 49.29

[1]LVSI: Lymph vascular space invasion; [2]Measured in cm.
*P <0.05.

Table 3 Surgery-related complications

Complications	ARH	LRH	N*
Cystotomy	0	2	2
Bowel injury	0	2	2
Ureterostenosis	1	0	1
Ureterovaginal fistula	0	1	1
Vesicovaginal fistula	0	2	2
Rectovaginal fistula	0	1	1
DVT**/PE	0	1	1
Intra-abdominal infection	3	1	4

*Some patients presented more than one complication.
**Deep venous thrombosis/Pulmonary embolism.

Results

From 1999 to 2004, 30 patients were included in this trial and underwent randomisation; 16 were submitted to LRH and 14 to ARH (Figure 1). No conversion to laparotomy occurred in the LRH group. Table 1 shows some patient characteristics; Table 2 shows the surgicopathological factors. There was no difference in the pelvic lymph node count between the LRH and ARH groups. Parametrial extension was significantly longer for patients submitted to LRH compared to ARH ($P = 0.07$ for the right parametrium and $P = 0.002$ for the left parametrium) (Table 2). There was no difference in operative time between the groups.

Table 3 shows all the transoperative and serious postoperative complications. Some patients presented with more than one complication. There were four transoperative complications, all in the LRH group. Two patients underwent inadvertent cystotomies during bladder dissections; both were recognised intraoperatively and sutured laparoscopically. One patient presented with left renal exclusion three months after surgery and underwent nephrostomy. Ten months after the LRH, she presented with a vesicovaginal fistula and underwent a successful surgical correction. Two years after LRH, the patient underwent a left nephrectomy. The other patient had an otherwise uncomplicated recovery.

One patient underwent a rectal injury that was sutured vaginally, and on the 14th postoperative day, she presented with a ureterovaginal fistula, which was initially unsuccessfully managed with a JJ catheter. She later underwent a successful correction of the fistula 30 days

Table 4 Transoperative and postoperative complications

Variables	ARH (14)	LRH (16)
Complication	5 (36%)	4 (25%)
No complication	8 (65%)	8 (75%)

ARH: Abdominal radical hysterectomy; LRH: Laparoscopic radical hysterectomy.

post-surgery. Another patient presented with a bowel injury unrecognised at the time of surgery and required an additional laparotomy the day after the LRH. An emergency descending colectomy and a colostomy were performed with washing of the cavity. She developed sepsis and deep venous thrombosis, and underwent a vesicovaginal fistula correction during a subsequent hospitalisation. She also presented with a rectovaginal fistula 24 months after LRH. This patient has been disease-free for 9 years and was fitted with a colostomy pouch. In the ARH group, one patient developed ureterostenosis after undergoing pelvic radiation indicated for positive pelvic lymph nodes; three patients group presented with abdominal sepsis and had favourable outcomes; and one was diagnosed with renal exclusion and underwent a nephrectomy.

Four (25%) patients in the LRH group presented with transoperative complications, but none of the patients in the ARH group presented with transoperative complications (Fisher's exact test = 0.10). Three patients (19%) in the LRH group presented with serious postoperative complications, and five patients (36%) presented with postoperative complications in the ARH group (Fisher exact test: 0.417). Table 4 and Additional file 1: Figure S1 shows the proportion of patients who presented with transoperative and serious postoperative complications (analysed together). In total, 36% (five) of the patients in the ARH group and 25% (four) of the patients in the LRH group presented with serious complications. The relative risk of presenting complications was 0.70, 95% CI (0.23–2.11), $P = 0.694$. No difference was found in the proportion of women who presented with transoperative or serious postoperative complications in this series.

Figure 2 shows postoperative pain curves. LRH group mean pain score was significantly lower than ARH after 36 h of observation ($P = 0.044$; mean difference score: 1.42; 95% CI: 0.04–2.80) (Figure 2). In the LRH group, one patient (6%) requested "on demand" morphine; in the ARH group, two patients (15%) requested "on demand" morphine (Fisher exact test 0.586) (See also Additional file 2: Figure S2).

Discussion

Laparoscopic radical hysterectomy had lower pain scores compared with abdominal radical hysterectomy in this series. Some studies comparing laparoscopic procedures in benign gynaecologic diseases with abdominal or vaginal procedures support our findings. A recent study randomised 41 patients who underwent laparoscopic hysterectomy (LH) and 41 patients who underwent vaginal hysterectomy (VH) for benign diseases. Postoperative pain was the primary endpoint and was measured using a 10-point verbal analogue scale (VAS). The LH group showed lower VAS pain scores than the VH group at 1, 3, 8, and 24 hours post-surgery [21]. A randomised study compared 19 patients who underwent laparoscopic myomectomy and 21 patients who underwent abdominal myomectomy. The pain scores were measured using a 10-point VAS. The laparoscopic myomectomy group had significantly lower pain scores than the abdominal

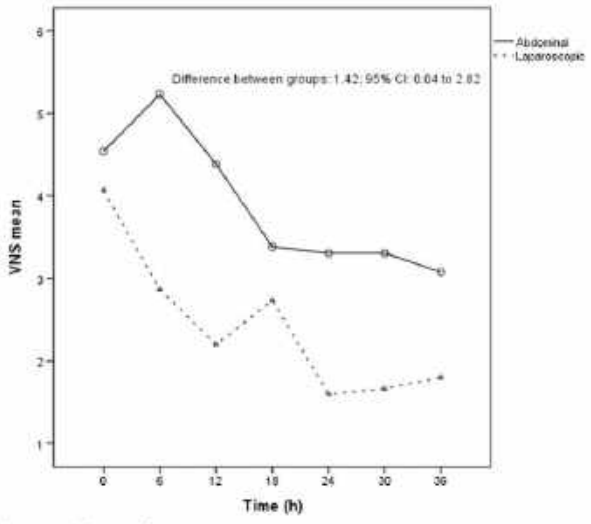

Figure 2 Postoperative pain scores 36 hours after surgery.

myomectomy group at 48 h (2.1 ± 1.5 – 4.0 ± 2.3, P >0.01) and 72 h (1.1 ± 3.7 P >0.01) post-surgery [7]. A meta-analysis compared laparoscopy versus laparotomy in benign ovarian tumours. The odds of being pain free at 24–48 hours post-surgery were significantly greater for laparoscopy (110 patients) than laparotomy (108 patients) at 24–48 hours post-surgery [5]. VAS and NRS are considered equally accurate in assessing postoperative pain and superior to a four-point verbal categorical rating scale [22].

The differences in the evaluated pain scores can be explained as follows. First, laparoscopic surgery uses electrosurgical devices for dissection and coagulation, whereas abdominal procedures require clamps, scissors and tying knots, particularly when used in abdominal radical hysterectomy. Therefore, ARH like other open techniques, could cause a wider inflammatory reaction [23,24]. Second, wider incisions are subjected to more tension, which can lead to more pain [25]. The use of morphine "on demand" can alter the results, but we believe that this use did not interfere with our results, as there was no significant difference in the morphine request between the LRH and ARH groups.

To our knowledge, there is no randomised controlled trial published on laparoscopic radical hysterectomy versus abdominal radical hysterectomy that must be performed entirely by laparoscopic approach [26,27]. A randomized controlled trial comparing laparoscopically assisted vaginal radical hysterectomy and ARH was published, where the inferior part of parametrium and paracolpium were transected by vaginal approach [28]. This study included patients with tumours <2 cm and postoperative pain was measured by the amount of analgesic consumption [28]. Postoperative acute pain can be reliably measured by NRS and VAS, which are considered correlated [29]. They function best for the patient's subjective feeling of present pain intensity. They may be used for worst, least, or average pain over last 24 h, or during the last week [22]. One of the strengths of the present study was the fact that assessment of present pain intensity as 5th vital sign was performed every 6 hours.

The current study shows that LRH and ARH do not differ in terms of postoperative complications. Four patients presented with transoperative complications, and three of those presented with postoperative complications that could be consequences of the first complication presented. Studies of laparoscopic surgery for benign gynaecologic conditions show a lower rate of complications than abdominal procedures. A recent meta-analysis comparing abdominal, laparoscopic and vaginal hysterectomy showed that laparoscopic hysterectomy showed fewer wound or abdominal infections [25]. A comparative retrospective study comparing LRH (n = 35) with ARH (n = 54) described 18% vs. 53%, respectively, febrile complication rates (P = 0.001) [12]. A prospective study with retrospective controls compared 50 women submitted to LRH with 48 women submitted to ARH (controls); a comparative rate of urinary complications was observed in both groups [30]. Different surgical skill levels can decrease the performance of a surgical technique [31]. One limitation of our study was the fact that patient inclusion occurred during the learning curve of the leading surgeon; performing this trial at the beginning of the main surgeon's training period most likely contributed to the LRH complication rate. A Finnish cohort of all hysterectomies performed in Finland from 1993 to 2005 reported a progressive decrease in serious complications for laparoscopic hysterectomies [32].

Oncological safety is always a concern in surgical studies. We included the parametrial extension measures to evaluate the surgical radicality, as proposed by Spirtos [8]. A retrospective comparative study comparing LRH (n = 34) with ARH (n = 37) found similar parametrial extensions: 3.8 cm (2.3–6.5) vs. 3.4 (1.7–7.0), P = 0.59; left parametrium 3.6 cm (2–6) vs. 3.5 (1.5–6.5), P = 0.82 [14]. A comparative retrospective study comparing LRH (n = 35) with ARH (n = 54) also found no differences in the parametrial extension [12]. Because we were not expecting any difference in the parametrial extension, we did not use any blinding. Longer parametrial extension measures for LRH could be explained by the magnification of tissue with the laparoscope, allowing a safer dissection near the bony pelvis.

Conclusions

LRH presented lower pain scores after 36 h of observation in this series. The complication frequency was similar. Further studies are required to ascertain a comparable long-term survival rate.

Additional files

Additional file 1: Figure S1. Transoperative and Postoperative complication.

Additional file 2: Figure S2. Distribution of Pain Scores.

Abbreviations

AHS: Abdominal radical hysterectomy; LRH: Laparoscopic radical hysterectomy; NRS: Numerical rating scale; VAS: Verbal analogue scale; VH: Vaginal hysterectomy.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Conception and design: LSC, LFL, ATS, ANK. Study coordination: LSC. Indusion and clinical data collection: LSC, LFL. Interpretation of data: LSC, LFL, ATS. Drafting and writing the manuscript: LSC, LFL. Revision of manuscript: LSC, LFL, ATS, ANK. All authors read and approved the final manuscript.

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Figure S1. Transoperative and postoperative complication.

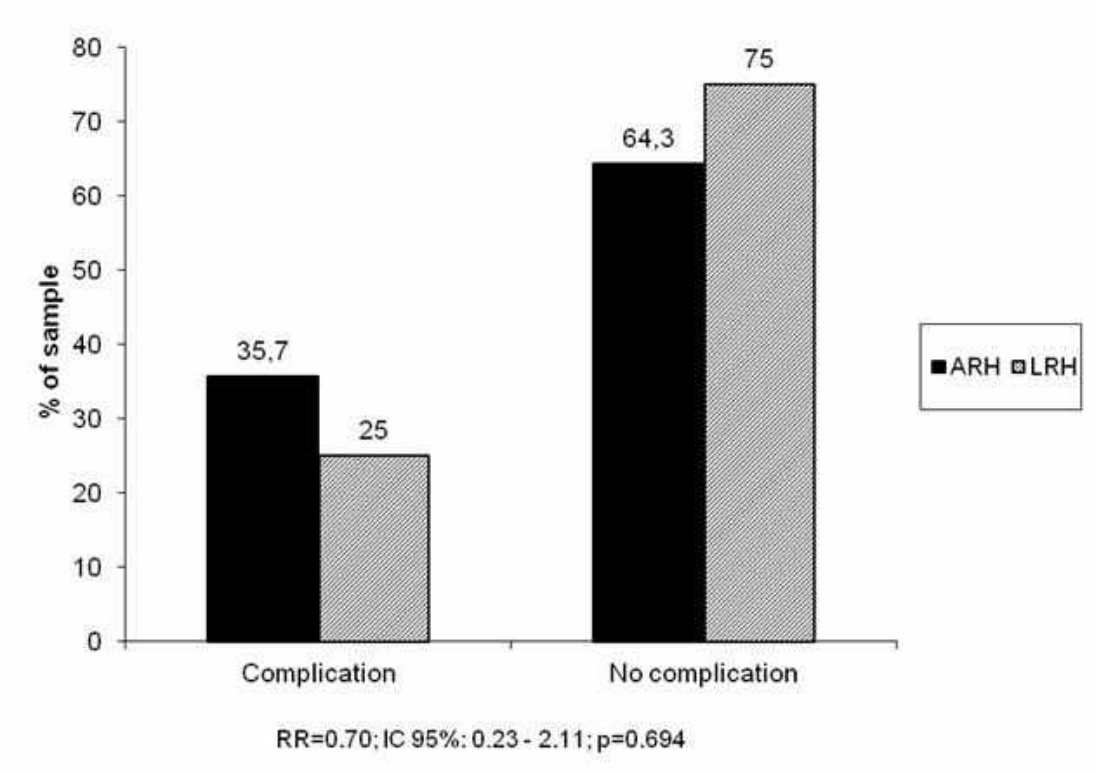
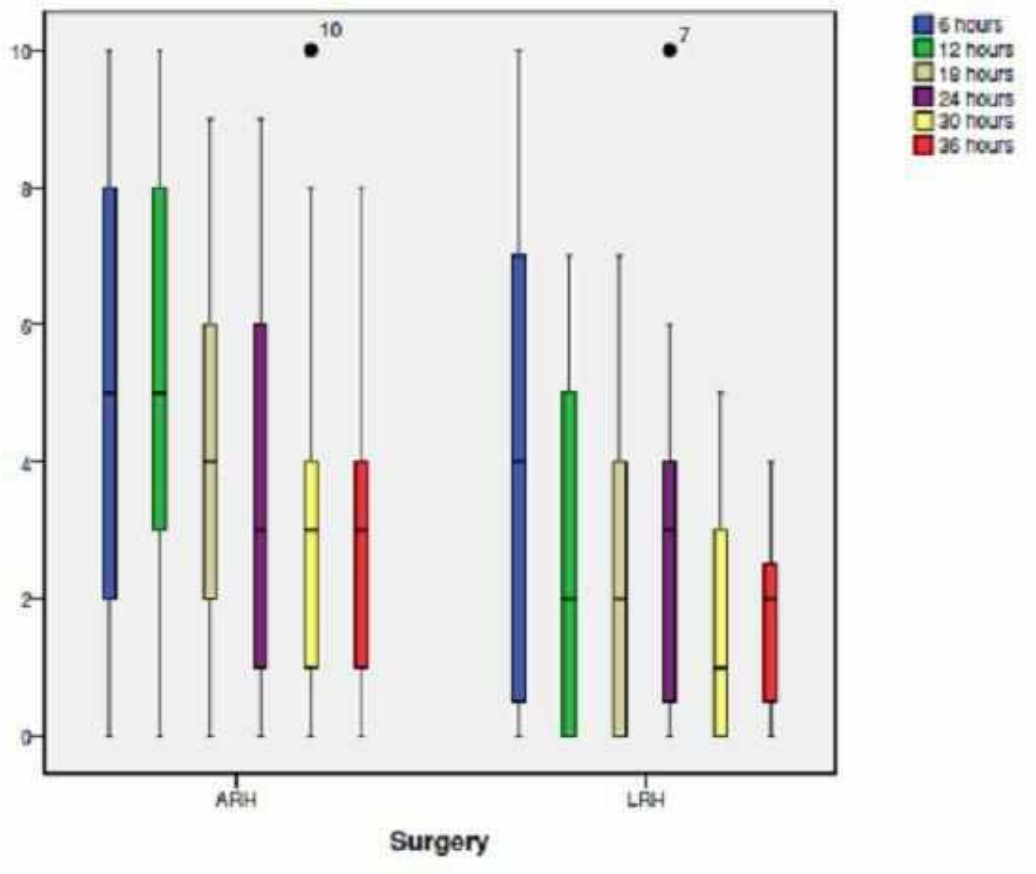


Figure S2. Distribution of Pain Scores.



5.4 ARTIGO IV – OVERALL AND DISEASE-FREE SURVIVAL AFTER LAPAROSCOPIC RADICAL HYSTERECTOMY AND ABDOMINAL RADICAL HYSTERECTOMY IN PATIENTS WITH EARLY CERVICAL CANCER: A SINGLE-CENTER RANDOMIZED CONTROLLED TRIAL[4]

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Condensation: Laparoscopic Radical Hysterectomy and Abdominal Radical Hysterectomy have similar overall and disease-free survival in this study.

[4] Artigo descrevendo os desfechos de longo prazo que será submetido à revista *European Journal of Obstetrics & Gynecology and Reproductive Biology*.

ABSTRACT

Objective: To compare overall and disease-free survival between Laparoscopic Radical Hysterectomy (LRH) and Abdominal Radical Hysterectomy (ARH) for early cervical cancer. **Study Design:** Single-center randomized controlled trial enrolled 30 cervical cancer patients who were clinically staged IA2 with lymph vascular invasion, IB and IIA according to the FIGO (International Federation of Gynecology and Obstetrics) classification, who underwent laparoscopic radical hysterectomy or abdominal radical hysterectomy ARH from 1999 to 2004. Postoperative pain was defined as the primary endpoint and was measured using a 10-point numerical rate scale. Both surgical techniques were executed by the same team. Secondary outcomes included intraoperative and postoperative complications, surgicopathological factors and 5-year survival. This paper aims to describe the secondary outcomes. **Results:** Thirty patients were randomized to undergo laparoscopic radical hysterectomy (16) or abdominal radical hysterectomy (14). There were no differences in demographic factors between groups. Three patients in the LRH group (18.8%) and 3 patients in the ARH group (21.4%) presented positive pelvic lymph nodes and received adjuvant radiotherapy (p = 1.00). The mean overall survival time was 74.74 months (CI 95%: 54.15-95.33) for the LRH group and 91.67 months (CI 95%: 74.97-108.37) for the ARH group (log-rank test = 0.300). The mean disease-free survival time was 81.07 months (CI 95%: 60.95-101.19) for the LRH group and 95.82 months (CI 95%: 80.18-111.47) for the ARH group (log-rank test = 0.371). The overall survival hazard ratio was 2.05 (CI 95%: 0.51-8.24), and the disease-free hazard ratio was 2.13 (CI 95%: 0.39-11.7), which were similar for both groups. **Conclusion**: Laparoscopic radical hysterectomy and abdominal had equivalent survival rates in this study. Our results suggest that laparoscopic radical hysterectomy is a safe alternative to abdominal radical hysterectomy.

Trial Registration: NCT01258413

Key Words: cervical cancer, laparoscopy, survival, randomized controlled trial

Introduction

Cervical cancer is the second most common cancer among women worldwide [1]. In Brazil, the estimated annual incidence is 19 cases per 100,000 women [2]. Radical hysterectomy with pelvic lymphadenectomy is one of the recommended treatments by FIGO (International Federation of Gynecology and Obstetrics) for early cervical cancer [3], which is traditionally performed by abdominal approach [4]. The cure rate for radical hysterectomy is up to 80% in patients in stages IB and IIA cervical cancer and tumor size less than 4 cm, and the cure rate is approximately 70% in patients with tumor size greater than 4 cm [5,6]. Tumor size, lymph vascular space invasion and positive nodes decrease survival [3,6] and require pelvic radiotherapy [3,7]. Radiotherapy and surgery have similar rates of survival when compared in randomized clinical trials [5,8].

The reported benefits of laparoscopic approach versus open approach for benign gynecological diseases include decreased postoperative pain and shorter hospital stay [9,10]. Previous studies have reported the safety of laparoscopic radical hysterectomy (LRH) [11-13]. Non-randomized comparative studies have demonstrated increased operative time [14-16], shorter hospital stay [14,15] and less postoperative infections [14] using LRH compared with to abdominal radical hysterectomy (ARH). Preliminary data from retrospective studies suggest an equivalent survival between two techniques [16,17,18]. A recent non-controlled study described 20-year follow-up of 240 patients after LRH and reported that the 5-year survival rates for IA2, IB1, IB2, and IIA cervical cancer were 100%, 82%, 66%, and 60%, respectively [19].

Methods

Detailed eligibility criteria, recruitment, endpoints, surgical techniques, anesthesia, analgesia, sample size calculation and randomization have been previously published [20]. This study was a single-center randomized controlled trial comparing LRH with ARH. Our hospital is a tertiary public hospital and the referred population had a low-income and had a difficult access to health services. Eligible patients were randomized to undergo either LRH or ARH. The primary outcome was defined as postoperative pain and the secondary outcomes were intraoperative and

postoperative complications, histopathological characteristics, overall survival and disease-free survival. This paper aims to describe the secondary outcomes.

Eligibility criteria

Inclusion criteria: Women who were enrolled in the study were at least 18 years of age, sought treatment at our facility and had histologically confirmed primary squamous, adenocarcinoma or adenosquamous cervical cancer that was diagnosed by biopsy or cervical conization and was clinically staged according to the FIGO classification as IA2 with lymph vascular invasion, IB or IIA [3].

Exclusion criteria: Patients with clinically advanced disease (IIB-IV), previous pelvic or abdominal radiotherapy, pregnancy or clinical diseases that would preclude one or both surgical approaches.

All surgeries were performed by the same team. To evaluate the oncological adequacy, the leading surgeon measured parametrial, uterosacral ligaments and vaginal cuff in the operation room [21].

Surgical techniques

***Laparoscopic radical hysterectomy*:** The patient was placed in Trendelenburg position and an uterine manipulator was placed. A Verres needle was placed for insufflation after supraumbilical insertion, and a 10-mm trocar was placed. Three 5-mm trocars were inserted. Infundibulopelvic ligament vessels were transected. The round was transected and broad ligaments were opened along the superior vesical artery, opening the paravesical space. The ureter was identified. The uterine vessels were transected at the point of origin from the internal iliac vessels. Parametrial tissue was transected close to the pelvic bone. Ureteres were unroofed.The vesicouterine ligament was transected to release parametrial tissue and vaginal wall. The rectal was incised and opening of pararectal space. Transection of the uterosacral ligaments was performed close pelvic wall. Blunt dissection of bladder. Transection of vagina and removal of specimen.

***Laparoscopic pelvic lymphadenectomy*:** right and left pelvic lymph nodes were dissected from the common external iliac artery along the genitofemoral nerve level to the circumflex iliac vein. Iliac internal nodes were removed. Obturator lymph

nodes were removed. These specimens were removed vaginally. The vaginal cuff was sutured laparoscopically.

Abdominal radical hysterectomy: ARH was performed according to the Piver III classification for radical hysterectomy [23]. Access to the abdominal cavity was obtained through a vertical midline incision.

Adjuvant radiotherapy/chemotherapy: Histopathological findings were used to determine the need for adjuvant postoperative treatment at the discretion of the responsible physician.

Assessment of perioperative complications and follow-up

Transoperative complications and severe postoperative complications were included in the same group. All patients were evaluated by the study team in the early postoperative period that managed all severe complications. The long-term follow-up was five years by the study team or personal physician, who was contacted periodically. Efforts were done in order to obtain outcome information from other sources, including contacting patients by telephone, contacting local general practioners, gynecologists or the family health clinic near the residence.

Sample size calculation and randomization

The Number Rating Scale score was considered the primary endpoint. We expected a 55% difference in the pain scale intensity between groups. The sample size was calculated using Epi Info, version 6.04b, software in a 1:1 sample, and we obtained 30 patients. Patients were assigned to groups by a random number table of 180 five-digit numbers, which were generated by an author (ATS) who did not participate in the patient selection, surgery or follow-up. After informed consent was obtained and before the surgery was performed, a random allocation number was determined by a telephone call. The authors who participated in patient selection and inclusion (LFL and LSC) did not have access to the random number table. The patients who were randomly allocated to even numbers were submitted to LRH, and patients with odd numbers were submitted to ARH.

Statistical analysis

An intention-to-treat-analysis was performed. Continuous variables with normal distribution were analyzed using Student´s *t*-test for independent samples and expressed as means and standard deviation, whereas non-normal distribution variables were analyzed using Mann-Whitney test and expressed as medians and percentiles. Discrete variables were compared using Pearson's chi-squared test and Fisher´s exact test. Disease-free survival (DFS) times were calculated in months from the date of surgery to the date of recurrence, censoring or the last follow-up exam. Overall survival (OS) time was calculated in months from the date of surgery to the date of death, censoring or the last follow-up exam. Survival curves and rates were calculated using Kaplan-Meier method, and differences in survival times between groups were compared using log-rank test. In Kaplan-Meier curves deaths related to the treatment were analyzed together with the deaths that were caused by the disease. Differences were considered statistically significant when the *p* values were < 0.05 in the two-sided test. Hazard ratio was the applied effect size. SPSS, version 18.0, was used for the statistical analysis.

Ethical considerations

The Ethics Committee of Grupo Hospitalar Conceição approved the study protocol in 1999. This protocol was registered at ClinicalTrials.gov, **Trial Registration: NCT01258413.**

Results

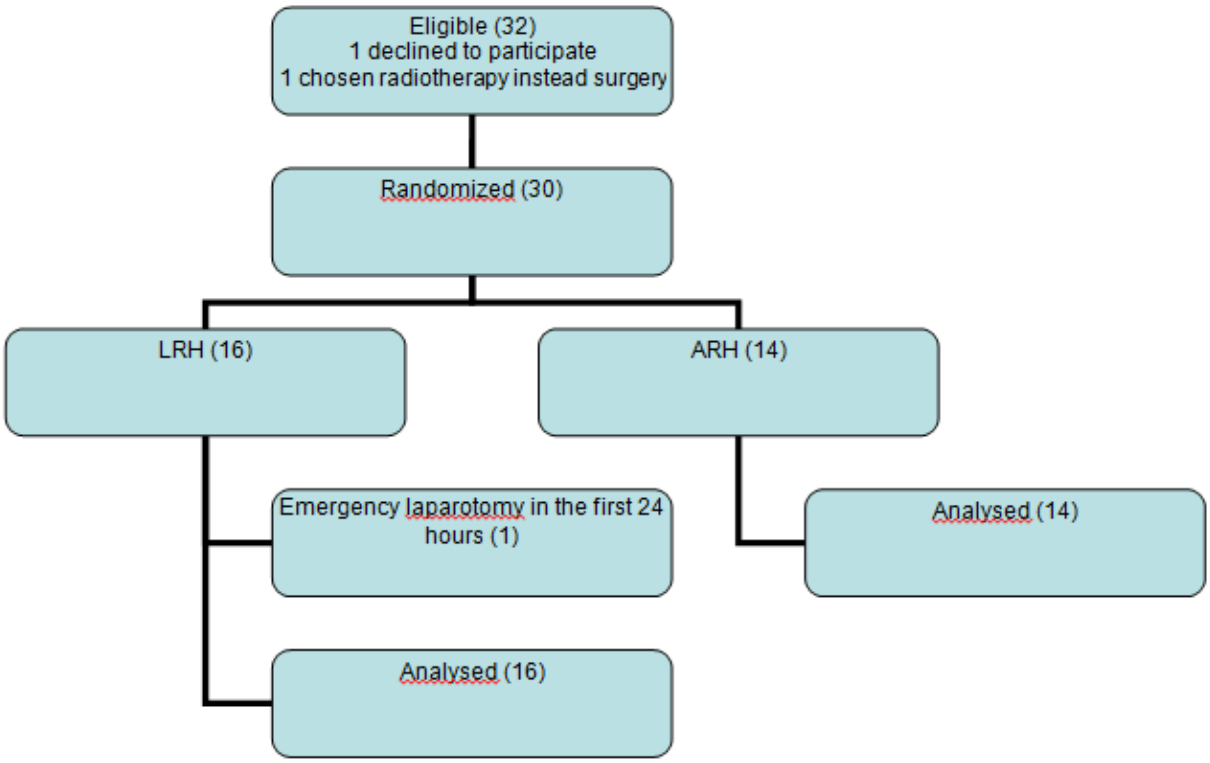

Figure 1. Study Flowchart

From 1999-2004, a total of 30 patients were included in this trial and underwent randomization. Sixteen patients were submitted to LRH, and 14 patients were submitted to ARH. No conversion to laparotomy occurred in the LRH group. The mean ages and most surgicopathological factors, were similar between groups (Tables 1 and 2). However, there was a significant difference between right and left parametrium measurements when LRH was compared to ARH (p = 0.007 for the right parametrium and p = 0.002 for the left parametrium) (Table 2). Three patients in the LRH group (18.8%) and 3 patients in the ARH (21.4%) group presented positive pelvic lymph nodes (p = 1.00), and all received adjuvant radiotherapy. At the time of the analysis, 6 patients (37.5%) in the LRH group and 3 (21.3%) patients in the ARH group had died (Fisher's exact test = 0.44). In both groups, 2 patients died of causes not related to cervical cancer recurrence or metastasis. In the LRH group, one patient died due to the consequences of bowel obstruction secondary to bowel stenosis as a complication of radiotherapy for treatment of primary bladder cancer. Another patient

died of breast cancer. There was no evidence of pelvic recurrence or metastasis in either of these patients. In the ARH group, one patient died due to the consequences of bilateral ureteral stenosis after pelvic adjuvant radiotherapy, that could not be managed by JJ ureteral catheter or percutaneuos nephrostomy, without evidence of pelvic recurrence or metastasis. In the Kaplan-Meier analysis, this patient was included in the group of deaths related to cervical cancer. The second patient died of sepsis without evidence of pelvic recurrence or metastasis. In 4 patients who died of cervical cancer recurrence or metastasis, palliative treatment was proposed, and 1 patient refused treatment. Three patients in the LRH (18.75%) group and 1 patient in the ARH (7.14%) group, experienced pelvic recurrence. These patients received palliative treatment and were alive at the time of the analysis (p = 0.602). All of the other patients were alive and free of disease.

Table 1: Patient characteristics.

Variables[a]	ARH (14)	LRH (16)	*P*
Age (years)	39.64 ± 6.23	36.19 ± 9.78	0.266
Number of pregnancies	3.5 (3.0 - 4.0)	2.5 (1.5 - 3.5)	0.028*
Smoking (n/%)	6 (42.9)	5 (31.3)	0.781
Previous conization(n/%)	6 (42.9)	8 (50)	0.980
Previous abdominal or pelvic surgery(n/%)	5 (35.7)	7 (43.8)	0.940

[a]Expressed as the mean ± standard deviation or the median (percentile 25-75) if quantitative and if categorical, n (%).
ARH: abdominal radical hysterectomy
LRH: laparoscopic radical hysterectomy

Table 2: Surgicopathological factors.

Variables	ARH (14)	LRH (16)	P
Squamous (n/%)	12 (85.7)	12 (75)	0.657
Adenocarcinoma(n/%)	2 (14.3)	4 (25)	0.657
LVSI (n/%)[a]	6 (42.9)	4 (25)	0.442
Lymph nodes(number)	19.43 ± 6.35	19.5 ± 8.41	0.979
Right parametria(cm)	4.14 ± 1.56	6.44 ± 2.59	0.007*
Left parametria(cm)	4.01 ± 1.42	6.33 ± 2.2	0.002*
Right uterosacral ligament(cm))	2.34 ± 0.91	2.78 ± 1.1	0.262
Left uterosacral ligament(cm)	2.26 ± 0.972	2.67 ± 1.1	0.315
Vaginal cuff(cm)	2.41 ± 1.18	3.17 ± 1.28	0.102
Operative time (min)	240.357 ± 26.852	264.375 ± 49.291	0.116

[a]LVSI: Lymph vascular space invasion.
cm: centimeters
min:minutes

Overall and disease-free survival

The survival outcomes did not differ statistically between groups **(Figs. 2 and 3)**. The mean overall survival time was 74.74 months (CI 95%: 54.15-95.33) for LRH group and 91.67 months (CI 95%: 74.97–108.37) for ARH group (log-rank test = 0.30). The mean disease-free survival time was 81.07 months (CI 95%: 60.95-101.19) for LRH group and 95.82 months (CI 95%: 80.18-111.47) for ARH group (log-rank test: 0.37). There were no differences in the overall and disease-free survival between the groups. The 5-year overall survival rate was 68.2% for LRH group and 78.6% for ARH group (log-rank test = 0.30). The 5-year disease-free survival rate was 73.1% for LRH group and 85.7% for ARH group (log-rank test: 0.37). The overall survival hazard ratio was 2.05 (CI 95%: 0.51-8.24), and the disease-free hazard ratio was 2.13 (CI 95%: 0.39-11.7).

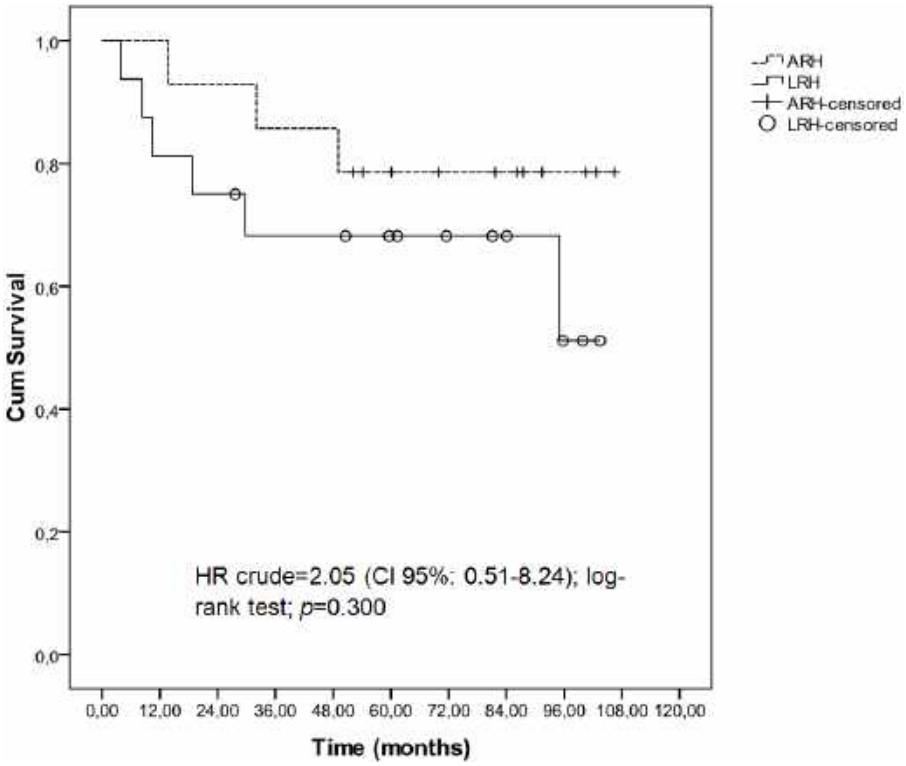

Figure 2.Kaplan Kaplan-Meier analysis of the overall survival rates in early cervical cancer patients who underwent laparoscopic radical hysterectomy or abdominal radical hysterectomy

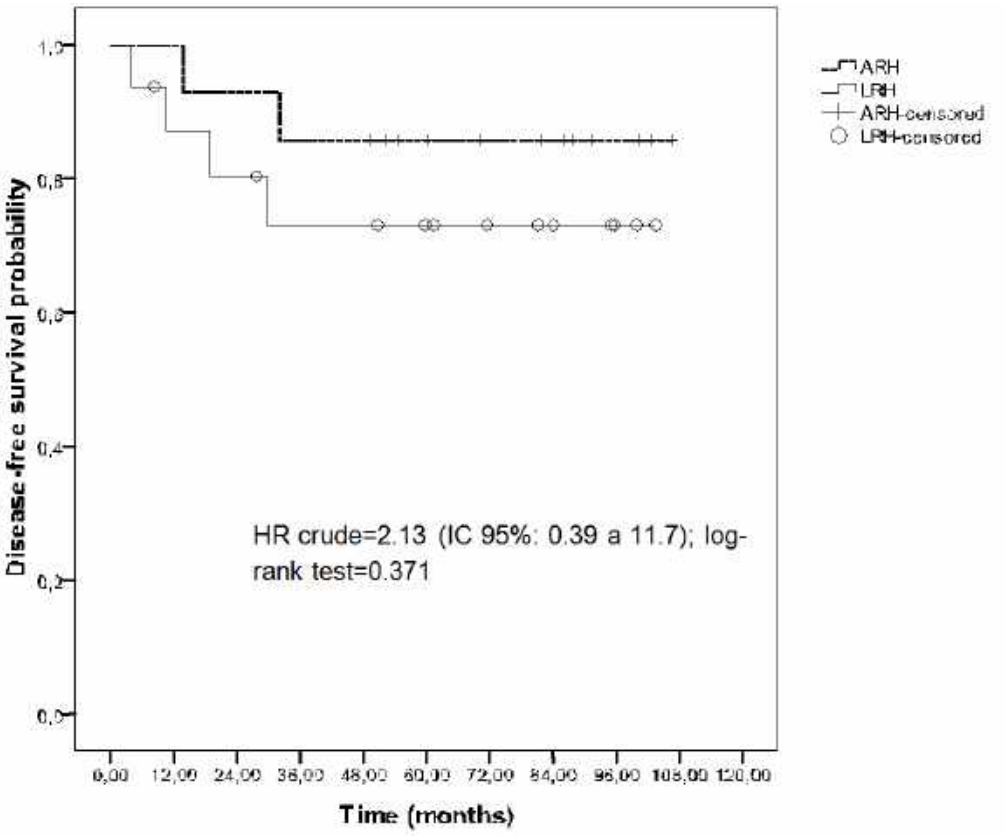

Figure 3 Kaplan-Meier analysis of the disease-free survival rates in early cervical cancer patients who underwent laparoscopic radical hysterectomy or abdominal radical hysterectomy.

Comment

Parametrium size [14,21,22], vaginal cuff size [14,21], lymph node count [14,15,17,21,23,24] and negative margins [14,23] were proposed as surrogate outcomes for evaluating the oncological adequacy of LRH. However, the survival and recurrence rates are the gold standard for the evaluation of a surgical technique [16,25]. In our study, there were no differences in the lymph node counts between the two techniques, and there was a significant difference in the parametrium sizes, which favored LRH (Table 2). Parametrium size has been compared in several studies, none of the studies found significant differences between the two techniques measured by the attending pathologist [14,23,24,26]. In our study, the parametria were measured by the main surgeon in the operation room, which is a limitation.

Several retrospective studies have compared LRH and ARH survival outcomes. A retrospective study compared 35 LRH and 54 ARH cervical cancer patients (IA2-IIB). The median follow-up duration was 15.2 months for ARH patients and 7.2 months for LRH patients. Two patients in the ARH group and 1 patient in the

LRH group experienced pelvic recurrence. Only one patient in this study had a stage IB2 tumor [14]. A retrospective study of patients with IB-IIA cervical cancer compared 90 patients who underwent LRH with 35 patients who underwent ARH. The median follow-up time was 26 months (range = 5-84 months). The recurrence rates for LRH and ARH were similar: 13.75% vs. 12% ($p > 0.05$), respectively. In addition, there were no differences in the mortality rates: 10% for LRH and 8% in ARH. ($p > 0.05$) A tumor diameter > 5 cm was an exclusion criterion [16]. In a retrospective study of patients with stage IA2-IB1 cervical cancer, 65 patients who underwent LRH were compared with 62 patients who underwent ARH. The median follow-up time was 52.5 months (range = 4-89 months) in LRH group and 71 months (range = 5-151 months) in ARH group. There were no differences in the disease-free survival times between groups (log-rank test, $p = 0.29$). In the LRH group, 92.4% of patients were free of disease compared with 93.3% of patients in the ARH group and no significant differences were found when recurrence rates were compared. ($p > 0.05$) Tumour size > 4 cm was an exclusion criteria [18]. A restrospective study compared patients underwent LRH (105), ARH (99), and laparoscopic assisted radical vaginal hysterectomy (LARVH) (89) with tumour size < 4cm. Median duration of follow-up time was 18 months for LRH group, 34 months for LRH group and 29 months for LARVH. There was no difference in disease free survival: 96,4 % in LRH, 91,9% in ARH and 92,1% in LARVH. [28]

Three case-control studies comparing LRH and ARH have been published to date. [15, 24, 27] In a case-control study that included IB-IIA patients, 30 patients who underwent LRH and 30 patients who underwent ARH were compared. The median follow-up time was 20 months for LRH patients and 41 months for ARH patients. A lesion > 4 cm was an exclusion criterion. One patient in ARH group presented a abdominal scar recurrence, treated successful with surgical resection and adjuvant chemotherapy [15]. The second one compared 24 IA2-IIA patients submitted to LRH and 48 patients submitted to ARH. Four (16,7%) patients in the LRH group and 10 (20.8%) patients in the ARH group presented positive pelvic lymph nodes. ($p<0,05$) Seven (29,2%) patients in LRH group and 13 (27,1%) patients in the ARH group underwent pelvic radiation or chemorradiation. ($p < 0,05$) Median follow-up time was 78 months for LRH group and 75 months for LRH group. Two (8,3%) patients in LRH (8,3%) group and four patients had recurrent disease. Disease-free survival was 90.5 % for LRH group and 93.3% for ARH group ($p=0,92$) [24] The study

compared IA2-IIB cervical cancer patients, submitted to LRH (263) and ARH (263). There were no differences in the recurrence risk: HR = 1.28 (CI 95%: 0.62-2.64) and death HR = 1.46 (CI 95%: 0.62-3.43). For patients with tumors > 2 cm, the risks of recurrence were similar: HR = 0.82 (CI 95%: 0.31-2.16) and death HR = 1.01 (CI 95%: 0.35-2.92). The 5-year recurrence-free survival rates for LRH and ARH patients were 92.8% and 94.4, respectively (p = 0.499). [27]

Most of the studies that have compared LRH and ARH survival have been based on small tumors [17, 28], short follow-up time [14-17], or both [17, 28]. The inclusion of tumours > 4 cm in our study reflected the regional practice pattern of that time, when the availability of brachytherapy was not widespread. [29] LRH and ARH patients had similar long-term oncological outcomes in our study and the survival was similar to studies that analyzed patients with lesions > 4 cm. In a non-controlled study that included stage IA2-IIB cervical cancer patients who underwent a laparoscopic radical hysterectomy, the survival rates for IB2 and IIA stage cancer were 66% and 60%, respectively [19] In most of the controlled studies in the literature, patients underwent MRI and/or a CT scan [15,17,18, 23, 24]; however, these exams were not available in our hospital at that time. These exams could help to exclude patients with early parametrial invasion,that can be underestimated by pelvic examination. [30, 31].

The first international randomized trial comparing LRH and ARH was initiated in 2008 with an estimated enrollment of 740 women with early stage cervical carcinoma. The estimated study completion date is 2017 [32]. The wider inclusion criteria in our study regarding tumor lesion size suggest that the survival outcomes of LRH are similar to those of ARH for stage IB cervical cancer patients. Our results support those from retrospective studies in which there was no difference in the survival, disease-free survival and recurrence rates between LRH and ARH patients. These findings suggest that LRH is oncologically safe, and published data on short-term outcomes suggest that LRH would be preferable over ARH.

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Conflict of Interest Statement: The authors declare no conflict of interest related to the subject of this paper

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6 CONCLUSÕES

1) As pacientes submetidas à histerectomia radical laparoscópica apresentaram menor de dor pós-operatória mensurada pela Escala Verbal Numérica do que as pacientes submetidas à histerectomia radical abdominal em 36 horas de pós-operatório, de maneira estatisticamente significativa.

2) As taxas de complicações perioperatórias das pacientes submetidas à histerectomia radical laparoscópica e das pacientes submetidas à histerectomia radical abdominal foram similares.

3) Não houve diferença estatisticamente significativa na sobrevida e na sobrevida livre de doença em cinco anos entre as pacientes submetidas à histerectomia radical laparoscópica e as pacientes submetidas à histerectomia radical abdominal.

4) Os achados deste estudo sugerem que a histerectomia radical laparoscópica é oncologicamente segura e que os menores escores de dor pós-operatória favorecem a escolha da histerectomia radical laparoscópica para o tratamento do carcinoma de colo uterino inicial.

ANEXO A – Parecer de aprovação do projeto de pesquisa pelo Comitê de Ética da Universidade Federal Ciências da Saúde de Porto Alegre

MINISTÉRIO DA EDUCAÇÃO
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COMITÊ DE ÉTICA EM PESQUISA
RUA SARMENTO LEITE, 245 – FONE: (51) 33038804
CEP 90050-170 – PORTO ALEGRE – RS - cep@ufcspa.edu.br

Of. 615/08-CEP

Porto Alegre, 14 de agosto de 2008

Ilmo. Sr.
Prof. Antônio Nochi Kalil
Nesta Universidade

Prezado Pesquisador

Informamos que seu projeto "Avaliação de pacientes com Carcionoma de colo de uterino inicial tratadas com Histerectomia radical por Laparotomia ou Laparoscopia – um ensaio clínico randomizado", Processo nº 338/07, foi avaliado pelo Comitê de Ética e Pesquisa, na reunião do dia 14 de agosto de 2008, sendo o projeto considerado aprovado, conforme parecer consubstanciado nº 661/08, anexo.

Outrossim, informamos que de acordo com o art. 4°, letra c do Regulamento do CEP, V.Sa. deverá nos encaminhar relatórios semestrais do desenvolvimento do projeto.

Atenciosamente,

Prof. José Geraldo Vernet Taborda
Coordenador do CEP/UFCSPA

ANEXO B – Parecer de aprovação do projeto de pesquisa pelo Comitê de Ética do Grupo Hospitalar Conceição

COMITÊ DE ÉTICA EM PESQUISA DO GRUPO HOSPITALAR CONCEIÇÃO
CEP - GHC
Porto Alegre, 10 de Novembro de 1999.

R E S O L U Ç Ã O

O Comitê de Ética em Pesquisa-CEP-GHC, em reunião ordinária realizada em 10/11/99, analisou o projeto de pesquisa:

Nº 65/99

Título: Tratamento do carcinoma de colo uterino por Vidêolaparoscopia.

Autor: Leo Limberger / Luciana Silveira Campos

Este trabalho, bem como o Termo de Consentimento Pós Informado, obteve o seguinte parecer **APROVADO**, de acordo com as Diretrizes e Normas Regulamentadoras de Pesquisas Envolvendo Seres Humanos (Resolução nº 196/96).

Atenciosamente

Dr. Sérgio R. G. Schmidt
Presidente Substituto
Comitê de Ética do GHC

ANEXO C – Normas para a publicação de artigos da revista *European Journal of Gynecology and Obstetrics & Reproduction*

ejog Obstetrics & Gynecology and Reproductive Biology

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After the accepted manuscript is published in an online issue: Any requests to add, delete, or rearrange author names in an article published in an online issue will follow the same policies as noted above and result in a corrigendum.

Manuscript categories
During submission the author must select a category from the following list: Review Article, Research Article, Book Review, Letter to the Editor. In preparing submissions, authors should check the general requirements for the preparation of manuscripts (see below).

Review articles
As well as invited articles we welcome submitted reviews on topics of current interest in obstetrics and gynecology. Reviews are allowed a maximum of 3500 words (excluding title page, abstract and references), 10 figures and 10 tables. The reference list should not exceed 3 pages.

Expert Opinions
These are generally ?invited? by the Editor-in-Chief but submission may be considered, with a maximum of 2000 words, 20 citations and 2 figures or 2 tables.

Research articles
For details, see below: ?General Requirements for the preparation of manuscripts?. There is a limit of 2500 words (excluding title page, abstract and references), 10 figures and 10 tables. The reference list should not exceed 3 pages.

Letters to the Editor are limited to a maximum of 600 words (excluding references, names and addresses of the signers, and the phrase "to the Editor"). Only one type of letter will be considered for publication:
Letter to the Editor - Brief Communication giving a brief case presentation or short report of a pertinent clinical observation. Please use the correct format following the criteria: max 600 words, max 5 references, max 1 table or 1 figure, no abstract, no keywords, no headings. The

information must be presented as a true Letter, e.g. starting with ?Dear Editor, we found that... etc.? Brief communications that do not meet this criteria will be returned to the author.

Announcements of major meetings and other significant activities should be sent to the Editor-in-Chief.

Editorial review process
Authors are responsible for following the criteria for the manuscript categories listed above before submitting the article to the Editorial Office. Articles not meeting these criteria will be rejected immediately without going through to peer review.

At submission authors will be asked to assign their article to a specialty subject area covered by the journal: obstetrics, maternal-fetal medicine, reproductive medicine and endocrinology, gynecology, gynecology oncology and urogynecology. All articles will undergo an initial review by an Advisory Board Editor expert in a particular specialty area. Articles will be assessed for:
- having sound methodological structure
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A standard abstract is required for review articles and expert opinions and has no sub headings. It is limited to 500 words for reviews and 300 words for expert opinions.

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APÊNDICE A – Termo de Consentimento Livre e Esclarecido

O tratamento cirúrgico do câncer do colo do útero é feito da mesma maneira há muito tempo e obtém ótimos resultados, apesar dos seus efeitos colaterais potenciais (efeitos indesejáveis que podem surgir com o tratamento, mesmo que ele seja realizado em condições ideais) significativos ao paciente e do período de convalescença relativamente longo. O objetivo deste trabalho é testar uma técnica cirúrgica mais moderna na tentativa de diminuir o desconforto e as complicações, mantendo taxas de cura semelhantes às do tratamento antigo.

Essa cirurgia já foi realizada em algumas pacientes recentemente em alguns hospitais ao redor do mundo e também pela nossa equipe nos hospitais de Porto Alegre e parece ser no mínimo tão segura quanto a anterior. Como essa cirurgia é bastante nova ainda, os resultados de acompanhamento dessas pacientes a longo prazo ainda não estão disponíveis. Pretendemos também acompanhar a evolução das pacientes que participarem a fim de obtermos resultados objetivos do tratamento a longo prazo.

Serão realizados os dois tipos de cirurgia: o tratamento consagrado e a nova técnica, e as pacientes serão sorteadas, podendo fazer qualquer um dos dois tipos, dependendo do sorteio. Todas as pacientes serão operadas e atendidas pela mesma equipe durante o período de internação e o pós-operatório, independentemente do tipo de cirurgia que venham a fazer.

É importante ficar claro que participar deste estudo não modificará nenhum outro aspecto do tratamento e que a decisão de não participar deste estudo também não implicará modificação do tratamento, sendo então as pacientes submetidas ao tratamento cirúrgico habitual.

Eu, _____, nacionalidade _____, estado civil _____, profissão _____; residente à _____; carteira de identidade número _____, reg. nº _____,

Declaro ter sido informado(a) pela equipe cirúrgica que a anamnese (história clínica) e os exames realizados revelaram que sou portadora de carcinoma de colo uterino passível de tratamento cirúrgico.

Declaro ter recebido a explicação sobre minha patologia, que para tentar tratar essa condição é necessário o seguinte procedimento: histerectomia radical com linfadenectomia pélvica por técnica videolaparoscópica ou laparotomia. Declaro ter sido informada que o tipo de tratamento a que me submeterei será definido por

sorteio. Declaro também estar ciente de que existe outra possibilidade de tratamento: a radioterapia, que apresenta taxas de cura semelhantes às da cirurgia.

Declaro ter sido orientada que durante o procedimento proposto poderão apresentar-se outras condições não reveladas pela investigação prévia, assim como poderão ocorrer condições imprevisíveis, ou que não eram conhecidas antes de iniciado o procedimento.

Declaro ter sido alertada que qualquer tipo de cirurgia pode acarretar riscos e consequências como, entre outros, danos vasculares, perda sanguínea, arritmias, isquemia miocárdica, infarto do miocárdio, choque anafilático, infecções, acidente vascular cerebral e inclusive morte.

Declaro ter sido informada que para realizar o procedimento proposto serão utilizadas substâncias químicas como anestésicos locais, entre outros, o que determinará minha exposição aos efeitos colaterais inerentes ao uso dessas drogas.

Declaro ter-me sido explicado o significado dos termos técnicos usados neste documento. Recebi informações claras a respeito deste tratamento e esclareci minhas dúvidas. Sei que em qualquer momento poderei solicitar novas informações e modificar minha decisão, se assim o desejar. O Dr. Leo Limberger e a Dra. Luciana Campos certificaram-me de que todos os dados desta pesquisa serão confidenciais, que meu tratamento não será modificado em função da minha participação nesta pesquisa e terei liberdade de retirar meu consentimento de participação nesta pesquisa.

Tendo tudo isso em consideração é que autorizo a equipe cirúrgica, seus assistentes, a realizarem o tratamento proposto. Caso tiver novas perguntas sobre o estudo posso chamar o Dr. Leo Francisco Limberger no telefone 3110913 ou a Dra. Luciana Campos no telefone 33512332 para qualquer pergunta sobre meus direitos como participante deste estudo.

Declaro que a autorização agora expressamente formulada, desde já, é extensiva a toda e qualquer condição que venha a revelar depois de iniciado(s) o(s) procedimento(s) inicialmente proposto(s).

Para que fique bem claro, assino livremente este documento.

Nome do paciente_____

Assinatura do paciente _____

Assinatura do pesquisador_____

Porto Alegre, _____ de _____ de _____.

APENDICE B – Inscrição do protocolo de pesquisa no *site* <http://clinicaltrials.gov>

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Trial record **2 of 6** for: laparoscopic radical hysterectomy
Previous Study | Return to List | Next Study

Laparoscopic vs Abdominal Radical Hysterectomy In Patients With Early Cervical Cancer

This study has been completed.

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ClinicalTrials.gov Identifier:
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First received: December 9, 2010
Last updated: December 22, 2010
Last verified: November 2010
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

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First Received Date ICMJE	December 9, 2010
Last Updated Date	December 22, 2010
Start Date ICMJE	November 1999
Primary Completion Date	February 2004 (final data collection date for primary outcome measure)
Current Primary Outcome Measures ICMJE **(submitted: December 10, 2010)**	postoperative pain measured by a 10 point numeric rating scale [Time Frame: around one week] [Designated as safety issue: No] The primary outcome is postoperative pain as measured by a 10-point numeric rating scale (NRS) during the postoperative period. Pain was assessed every six hours by nursing staff during a patient's usual postoperative care. The nursing staff was not aware of the study objective.
Original Primary Outcome Measures ICMJE	*Same as current*
Change History	Complete list of historical versions of study NCT01258413 on ClinicalTrials.gov Archive Site
Current Secondary Outcome Measures ICMJE **(submitted: December 10, 2010)**	• Intraoperative, perioperative and postoperative complication [Time Frame: 30 days or five years] [Designated as safety issue: Yes] 1 Intraoperative outcomes included the following: operative time (minutes), injuries to the ureter, bladder, bowel or vessels and anaesthesia complications requiring blood transfusion.2. Early (< 30 days) or late postoperative events and findings during the hospital stay or after included the following: hospital stay duration (days), complications. Surgical or clinical findings that could be attributable to the treatment in five years of follow up 74 Clinical or surgical findings that could be attributable to the treatment or the disease at five years of follow-up. • Surgicopathological outcomes [Time Frame: postoperatively] [Designated as safety issue: No] outcomes included the following: histological type, surgical margins, lymph node status and lymph node number, all assessed by pathologists with expertise in gynaecologic oncology. In addition, parametrial and vaginal cuff width (centimetres) was assessed by the first surgeon in the operating room, before tissue processing. • Overall survival and disease-free survival [Time Frame: five years] [Designated as safety issue: No] Clinical status in the last visit recorded; Date and location of the first recurrence or metastasis. Time frame: five years from surgery
Original Secondary Outcome Measures ICMJE	*Same as current*
Current Other Outcome Measures ICMJE	*Not Provided*
Original Other Outcome Measures ICMJE	*Not Provided*

Descriptive Information	
Brief Title ICMJE	**Laparoscopic** vs Abdominal **Radical Hysterectomy** In Patients With Early Cervical Cancer
Official Title ICMJE	**Laparoscopic** vs Abdominal **Radical Hysterectomy** With Pelvic Lymphadenectomy in Patients With Early Cervical Cancer: A Randomized Clinical Trial
Brief Summary	The purpose of this study is to determine whether **laparoscopic radical hysterectomy** for early cervical cancer will has decreased postoperative pain intensity compared to abdominal **radical hysterectomy** with similar postoperative complications and survival rates.
Detailed Description	Background: Radical hysterectomy with pelvic lymphadenectomy is one of the FIGO (International Federation of Gynecology and Obstetrics) recommended treatments for early cervical cancer. The objective of this study was to compare radical hysterectomy by laparoscopic approach and open radical hysterectomy in a single center randomized clinical trial. Nevertheless, there are no finished randomized controlled trials comparing laparoscopic radical hysterectomy and abdominal radical hysterectomy although there is an ongoing trial. Methods: Were enrolled 30 IA2 with lymph vascular space invasion and IB cervical cancer patients. Postoperative pain intensity was defined as primary endpoint and pain intensity was measured by a 10-point numeric rating scale. Secondary outcomes were: intraoperative and other postoperative outcomes, histopathological outcomes and 5-year follow-up. Data analysis is being done at this moment.
Study Type ICMJE	Interventional
Study Phase	Phase 3
Study Design ICMJE	Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Masking: Open Label Primary Purpose: Treatment
Condition ICMJE	• Cervical Cancer • Postoperative Pain
Intervention ICMJE	• Procedure: **Laparoscopic Radical Hysterectomy** + pelvic lymphadenectomy uterus, upper 1-2cm of vagina , parametrial tissue and uterosacral ligament + pelvic lymphadenectomy are removed by **laparoscopic** approach • Procedure: Abdominal **radical hysterectomy** uterus, upper 1-2cm of vagina , parametrial tissue and uterosacral ligament + pelvic lymphadenectomy are removed by abdominal approach
Study Arm (s)	• Experimental: **Laparoscopic Radical Hysterectomy** uterus, upper 1-2cm of vagina , parametrial tissue and uterosacral ligament are removed + pelvic lymphadenectomy Intervention: Procedure: **Laparoscopic Radical Hysterectomy** + pelvic lymphadenectomy • Active Comparator: Abdominal **radical hysterectomy** uterus, upper 1-2cm of vagina , parametrial tissue and uterosacral ligament are removed + pelvic lymphadenectomy Intervention: Procedure: Abdominal **radical hysterectomy**
Publications *	*Not Provided*

* Includes publications given by the data provider as well as publications identified by ClinicalTrials.gov Identifier (NCT Number) in Medline.

Recruitment Information	
Recruitment Status ICMJE	Completed
Enrollment ICMJE	30
Completion Date	February 2009
Primary Completion Date	February 2004 (final data collection date for primary outcome measure)
Eligibility Criteria ICMJE	Inclusion Criteria: • Women of 18 years or older referred to our service with histologically confirmed primary squamous, adenocarcinoma or adenosquamous cervical cancer diagnosed by biopsy or cervical conization,

	clinically FIGO (International Federation of Gynecologic and Obstetrics) staged IA2 with lymph vascular invasion, IB and II A. Exclusion Criteria: • Patients with clinically advanced disease (IIB-IV), previous pelvic or abdominal radiotherapy, pregnancy, clinical diseases that would preclude one or both surgical approaches.
Gender	Female
Ages	18 Years and older
Accepts Healthy Volunteers	No
Contacts ICMJE	*Contact information is only displayed when the study is recruiting subjects*
Location Countries ICMJE	Brazil

Administrative Information	
NCT Number ICMJE	NCT01258413
Other Study ID Numbers ICMJE	CEPGHC: 65/99
Has Data Monitoring Committee	No
Responsible Party	Dr. Leo Franscisco Limberger, Hospital Nossa Senhora da Conceição
Study Sponsor ICMJE	Hospital Nossa Senhora da Conceicao
Collaborators ICMJE	*Not Provided*
Investigators ICMJE	Principal Investigator: Leo F Limberger, M.D. Hospital Nossa Senhora da Conceição
Information Provided By	Hospital Nossa Senhora da Conceicao
Verification Date	November 2010

ICMJE **Data element required by the International Committee of Medical Journal Editors and the World Health Organization ICTRP**