Adjuvant radiotherapy in early stage endometrial cancer

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Summary

Objective: To compare the rates of overall survival (OS), disease-free survival (DFS) and toxicity in different techniques of postoperative radiotherapy for stage IA endometrioid adenocarcionoma of endometrium, histological grades 1and 2. **Methods:** A historical comparison between treatment regimens was performed, and 133 women with a minimum follow-up of 5 years were included. Teletherapy (TELE group), with 22 patients treated from 1988 to 1996, with a 10 MV linear accelerator, average dose 46.2 Gy. Low dose rate brachytherapy (LDRB group) was performed between 1992 and 1995, in 19 women, with an insertion of Cesium 137, at a 60 Gy dose. Fourteen women operated between 1990 and 1996 did not receive radiotherapy (NO RT group). High dose rate brachytherapy was performed in 78 patients (HDRB group), from 1996 to 2004, in five weekly 7 Gy insertions, prescribed at 0.5 cm from the vaginal cylinder. **Results:** The 5-year disease-free survival was 94.6% for the HDRB group, 94.1% for the LDRB group, 100% for the TELE group and NO RT groups ($p = 0.681$). The 5-year overall survival was 86.6% for the HDRB group, 89.5% for the LDRB group and 90% for the TELE group and NO RT groups ($p = 0.962$). Grades 3-5 late toxicity was 5.3% in LDRB group and 27.3% for the TELE group ($p < 0.001$). **Conclusion:** Patients submitted to adjuvant teletherapy showed very high toxicity, which contraindicates that treatment for those patients. There may be a role for adjuvant HDRB, but randomized controlled trials are still needed to evaluate its benefit.

Keywords: Genital neoplasms, female; radiotherapy, adjuvant; brachytherapy; endometrial neoplasms.

Resumo

Radioterapia adjuvante para câncer do endométrio estádio inicial

Objetivo: Comparar as taxas de sobrevida global (SG), sobrevida livre de doença (DFS) e de toxicidade em diferentes técnicas de radioterapia pós-operatória para adenocarcionoma endometrioide do endométrio estádio IA, graus histológicos 1 e 2. **Métodos:** Realizou-se uma comparação histórica entre regimes de tratamento, incluindo 133 mulheres com seguimento mínimo de cinco anos. Teleterapia (grupo TELE), com 22 pacientes, de 1988 a 1996, tratadas com acelerador linear 10 MV, dose média de 46,2 Gy. Braquiterapia de baixa taxa de dose (grupo LDRB), realizada entre 1992 e 1995, em 19 mulheres, com uma inserção de Césio 137, dose de 60 Gy. Quatorze mulheres operadas entre 1990 e 1996 não receberam radioterapia (grupo NO RT). Braquiterapia de alta taxa de dose foi realizada em 78 pacientes (grupo BATD), 1996-2004, cinco inserções semanais de 7 Gy, a 0,5 cm do cilindro vaginal. **Resultados:** A DFS em cinco anos foi de 94,6% para o grupo BATD, 94,1% para o grupo LDRB, 100% para os grupos TELE e RT ($p = 0,681$). A sobrevida global em cinco anos foi de 86,6% para o grupo BATD, 89,5% para o grupo LDRB e 90% para os grupos TELE e NO RT ($p = 0,962$). A toxicidade tardia graus 3-5 foi de 5,3% no grupo LDRB e 27,3% para o grupo TELE ($p < 0,001$). **Conclusão:** Pacientes submetidos à teleterapia adjuvante apresentaram toxicidade muito elevada, o que contraindica o tratamento para essas pacientes. Pode haver um papel para a BATD adjuvante, mas estudos controlados randomizados são necessários para avaliar seu benefício.

Unitermos: Neoplasias dos genitais femininos; radioterapia adjuvante; braquiterapia; neoplasias do endométrio.

Study conducted at the Departament of Tocogynecology, Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brazil

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Introduction

Surgery is the primary treatment for stage 1 endometrial cancer, and radiotherapy can be used as adjuvant treatment. Medical literature has not defined the best adjuvant treatment for stage 1A endometrial cancer, histological grades 1 and 2[1]. Teletherapy is advocated by some authors, high dose rate brachytherapy (HDRB) by others, and also low dose rate brachytherapy (LDRB) has been described[2-7]. There are also authors who question the use of any adjuvant radiotherapy[8,9].

A meta-analysis evaluated the benefit of adjuvant teletherapy in cancer of endometrium stage I. With four randomized controlled trials included, 1,770 patients were analyzed, with 870 in the treatment group and 900 in the control group. There was a reduction of 72% in the risk of loco-regional recurrence, $p < 0.00001$, with NNT (number needed to treat) of 16.7 to prevent a recurrence. There was no difference between the rates of distant recurrence, overall survival, and deaths, but higher toxicity[10].

There are no randomized controlled trials comparing adjuvant brachytherapy and teletherapy for endometrial carcinoma, stage IA, histological grades 1 and 2 carriers. The question remains, whether vaginal brachytherapy can bring local control benefit comparable to teletherapy. We can not say if the toxicity for these treatments is similar, just for lack of such clinical trials. Given these considerations, this study was conducted, as a retrospective analysis of sequential series. It reports comparative results of endometrial cancer patients, stage IA, grades 1 and 2, treated with LDRB, HDRB and teletherapy.

Methods

Patients

This is a historical comparison between treatment regimens. Between 1988 and 2004, 133 women with uterine endometrioid adenocarcinoma, FIGO stage IA (less than half myometrial invasion), histological grades 1 and 2, underwent surgery at the department of Gynecology and Obstetrics, School of Medicine, *Universidade Estadual de Campinas*, Campinas, Brazil. Before 1996, some of them received no adjuvant treatment, and others were submitted to teletherapy or LDRB. In 1996, with the introduction of HDRB, all patients received adjuvant HDRB. These patients had a minimum follow-up of 5 years, and their treatment results were retrospectively evaluated, with progression-free survival, overall survival and toxicity as endpoints. Table 1 summarizes patient characteristics.

The HDRB group with 78 patients and mean age 62.9 years was treated between 1996 and 2004 with Nucletron micro-Selectron HDRB with the largest vaginal cylinder possible. They received five weekly 7 Gy fractions, prescribed to 0.5 cm of the applicators, 4 cm length, total dose of 35 Gy. This fractioning regimen was calculated based on Dale radiobiological equations[11]. Bladder and rectum doses were not calculated.

The LDRB group, with 19 patients and a mean age 64.9 years was treated between 1992 and 1995, received one insertion of LDRB, with Cesium 137, in vaginal vault, receiving a dose of 60 Gy at the cilinder, in the upper two thirds of vaginal cuff length.

Table 1 – Patient characteristics according to treatment group

Characteristic	HDRB	LDRB	TELE	NO RT#	p value
Patient number	78	19	22	14	–
Age – mean	62.9	64.9	62.4	63.1	
(standard deviation)	(8.4)	(7.1)	(9.5)	(8.8)	0.783*
Follow-up in months-mean	88.9	118.1	99.0	102.6	
(standard deviation)	(35.3)	(49.9)	(48.7)	(58.1)	0.057*
Lost to follow-up	4	0	3	2	
(%)	(6.3)	(0.0)	(13.6)	(9.1)	0.1 54+
Surgery (%)					
Hysterectomy + lymphadenectomy	50 (64.1)	18 (94.7)	15 (68.2)	8 (66.7)	
Hysterectomy	28 (35.9)	1 (5.3)	7 (31.8)	4 (33.3)	0.0 77+
Histological grade (%)					
I	48 (61.5)	9 (47.4)	6 (27.3)	5 (45.5)	
II	30 (38.5)	10 (52.6)	16 (72.7)	6 (54.6)	0.0 35+
Linfovascularinvasion (%)					
Positive	1 (1.3)	0 (0.0)	3 (13.6)	0 (0.0)	
Negative	77 (98.7)	19 (100.0)	19 (86.4)	12 (100.0)	0.018+

*ANOVA test; + chi-square test; # two patients died from surgery complications and were excluded from analysis.

Teletherapy group, 22 patients with a mean age 62.4 years, was treated between 1988 and 1996, with photon beam energy in a 10 MV megavoltage linear accelerator, using the four-field technique. Anteroposterior superior borders fields were between L4 and L5, inferior borders at the obturator foramen and lateral limits were 1.5 cm lateral to pelvic brim. Lateral fields had anterior borders at the pubic symphysis, and posterior borders between S2 and S3. Doses ranged from 45 to 52.2 Gy (mean: 46.2 Gy), in daily 1.8-2 Gy, fractions 5 times a week.

NO RT group, with 14 patients, mean age 63.1 years, operated between 1990 and 1996, had no adjuvant radiotherapy.

Follow-up and statistical analysis

After treatment, patients were reassessed every four months during the first two years, every six months until the fifth year, and annually thereafter, on the basis of clinical examination, oncotic colpocytology, pelvic ultrasound and laboratory tests. They were followed up for at least five years. Overall survival (OS) time was measured from the date of surgery to the date of death or the most recent follow-up, progression free survival (PFS) as period from time of surgery to date of first documented evidence of progressive disease. Treatment toxicity was graded according to toxicity criteria of the radiation therapy oncology group (RTOG)[12].

The Kaplan-Meier method was used to generate survival curves to compare treatment results. A Log-Rank test was used to analyze the results. Patients without recurrent disease were censored at their last follow-up visit or death. For all statistical tests, $p < 0.05$ was considered significant. All statistical analyses were performed using SPSS software (version 11.01. for windows) Leadtoolsq 1991-2000 LEAD Technologies Inc.

This study was reviewed and approved by the research ethics committee of the institution.

Results

Table 2 shows the patients status by treatment group, at the end of follow-up. The 5-year disease-free survival was 94.6% for HDRB group, 94.1% for LDRB group, 100% for TELE group and 100% for the NO RT group ($p = 0.681$).

The 5-year overall survival was 86.7% for the HDRB group, 89.5% for the LDRB group, 89.9% for the TELE group and 90.1% for the NO RT group.

Toxicity was described using the criteria of the Radiation therapy oncology group (RTOG)[12]. Grades 1 and 2 radiotherapy-related late toxicity was 18% for HDRB group, 10.5% for the LDRB group, and 1% for the TELE group. Grades 3-5 late toxicity did not occur in HDRB group, but was 5.3% in LDRB group and 27.3% for the TELE group ($p < 0.001$). There was no significant statistical relation between lymphadenectomy and higher toxicity, and the worsening of severe toxicity was related to radiation dose above 45 Gy ($p < 0.001$). Table 3 reports toxicity details.

According to Cox, acute lower G.I. toxicity, including pelvis is graded as 0 when there is no change. Grade 1 with increased frequency or change in quality of bowel habits, not requiring medication, rectal discomfort not requiring analgesics. Grade 2, includes diarrhea requiring parasympatholytic drugs, mucous discharge not necessitating sanitary pads, rectal or abdominal pain requiring analgesics. Grade 3 diarrhea requiring parenteral support, severe mucous or blood discharge necessitating sanitary pads, abdominal distention. Grade 4, acute or subacute obstruction, fistula or perforation, GI bleeding requiring transfusion, abdominal pain or tenesmus requiring tube decompression or bowel diversion. Grade 5, death related to radiation effects.

The acute genitourinary toxicity is graded as 0, when there is no change. Grade 1, frequency of urination or nocturia, twice pretreatment habit, dysuria, urgency not requiring medication. Grade 2, frequency of urination or nocturia, that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic. Grade 3, frequency with urgency and nocturia hourly or more frequently, dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross hematuria with or without clot passage. Grade 4, hematuria requiring transfusion, acute bladder obstruction not secondary to clot passage, ulceration, or necrosis. Grade 5, death related to radiation effects.

Cronic GI toxicity, grade 0 no change. Grade 1 mild diarrhea; mild cramping; bowel movement 5 times daily; slight rectal discharge or bleeding. Grade 2, moderate diarrhea and colic; bowel movement > 5 times daily;

Table 2 – Survival and estimated relative risks by treatment group

Treatment	Patients (n)	OS+ (%) at 5 years	Hazards ratio* (95% CI)	DFS# (%) at 5 years	Hazards ratio* (95% CI)
HDRB	78	86.7	1.0	94.6	1.0
LDRB	19	89.5	0.8 (0.2-3.8)	94.1	0.5 (0.6-4.3)
TELE	22	89.9	0.8 (0.2-3.6)	100.0	0.5 (0.7-3.7)
NO RT	12	90.1	0.7 (0.9-6.2)	100.0	0.9 (0.1-6.5)

* Hazards ratio and 95% confidence intervals obtained from a Cox model; + overall survival; # disease-free survival.

Table 3 – Radiation toxicity by treatment group

Characteristic	HDRB	LDRB	TELE	p value*
Acute toxicity (%)				0.239
Absent	66 (84.6)	18 (94.7)	21 (95.4)	
Grades 1-2+	12 (15.4)	1 (5.3)	1 (4.6)	
Acute toxicity organs (%)				0.153
Gastrointestinal	0 (0.0)	0 (0.0)	1 (4.6)	
Bladder	8 (10.3)	1 (5.3)	0 (0.0)	
Vagina	4 (5.1)	0 (0.0)	0 (0.0)	
Late toxicity (%)				< 0.001
Absent	64 (82.0)	16 (84.2)	15 (68.2)	
Grades 1-2+	14 (18.0)	2 (10.5)	1 (4.6)	
Grades 3-5+	0 (0.0)	1 (5.3)	6 (27.3)	
Late toxicity organs (%)				
Gastrointestinal	10 (12.8)	1 (5.3)	5 (23.0)	
Bladder	1 (1-3)	2 (10.5)	1 (4.6)	
Vagina	3 (3.9)	0 (0.0)	1 (4.6)	0.384

*chi-square test; +using the toxicity criteria of the radiation therapy oncology group (RTOG).

excessive rectal mucus or intermittent bleeding. Grade 3, obstruction or bleeding, requiring surgery. Grade 4 necrosis, perforation and fistula. Grade 5, death related to radiation effects.

Cronic genitourinary toxicity is grade 0 when there is no change. Grade 1 slight epithelial atrophy; minor telangiectasia (microscopic hematuria). Grade 2 moderate frequency; generalized telangiectasia; intermittent macroscopic hematuria. Grade 3 severe frequency and dysuria, frequent hematuria; reduction in bladder capacity (< 150 cc). Grade 4, necrosis, contracted bladder (capacity < 100 cc), severe hemorrhagic cystitis. Grade 5, death related to radiation effects[12].

Discussion

The current study used a time-series design to evaluate outcomes and toxicity in adjuvant treatment for FIGO stage IA endometrial adenocarcinoma, histological grades 1 and 2. There was no difference in DFS and OS for the different radiotherapy regimens, even when compared to no radiotherapy at all.

Aalders *et al.*[13] published a randomized study with 540 patients, FIGO old stages IB and IC, including IB, histological grade 1[14]. The patients were operated without lymphadenectomy and received low dose rate brachytherapy in vaginal vault, dose of 6,000 cGy, then randomized into two groups: observation and pelvic teletherapy, dose of 4,000 cGy. In a 3 to 10 years follow-up, the group that received teletherapy showed lower pelvic and vaginal recurrence (1.9 x 6.9%, p < 0.01) but no improvement in overall survival.

The PORTEC study[15] included 715 patients with stage I, from 19 radiotherapy centers. They were submitted to surgery, without lymphadenectomy, but with palpation and biopsy of suspicious nodes. After the surgery, they were randomized between adjuvant teletherapy with 4,600 cGy or no other treatment. In a median follow-up of 52 months, there was a significant reduction of local recurrence in five years (4% x 14%, p < 0.001), but worsening toxicity. There was no significant difference in survival at five years (81% x 85%, p = 0.31)[16]. Data of this study was updated to a mean 94 months follow-up, with local recurrence at 10 years of 5% in the group with radiotherapy and 14% in the group without radiotherapy (p < 0.0001) and overall survival at 10 years of 66% for radiotherapy group and 73% for the group without radiotherapy (p = 0.09), showing again the radiation influence on local control, but without impact on overall survival, even excluding the patients stage IA grade 1 after pathological review.

The GOG 99[17] study included 448 women with old FIGO stages IB, IC and II (occult disease), and 392 (88%) were considered eligible. The surgery included pelvic and para-aortic lymphadenectomy, and subsequent randomization to teletherapy with 5,040 cGy to pelvis or no other additional treatment. With a mean follow-up of 68 months, the group submitted to external radiotherapy had a reduction in recurrence risk by 58% (p = 0.007). The estimated survival at four years for the control group was 86% and 92% for the group that received radiotherapy. This improvement in survival did not reach statistical significance (p = 0.557). The authors concluded that radiotherapy reduces the risk of recurrence, but should

be used only in women aged more than 70 years, in tumors with linfovascular invasion, stage IC[14], histological grades 2 and 3.

Our series failed to show an association between the different adjuvant radiotherapy techniques and improvement in local control or overall survival. An important point to note is that patients included in our study had better prognostic factors than those described in the papers cited above. Therefore, the measurement of a benefit, if any, may require a much larger number of women to be included, and perhaps a longer follow-up is needed. Actually, this study had no statistical power to compare these outcomes, due to the very low number of events.

Regarding toxicity, Piver and Hempling[7] reported that among 92 patients treated with low dose rate brachytherapy, 1% had severe toxicity, and of 41 submitted to teletherapy, 9% had severe toxicity. Cengiz *et al.*[4] described 9% of grade 3-4 toxicities with teletherapy in 78 patients and no cases of grade 3-4 toxicity in 31 women treated with low and high dose rate brachytherapy. Aalders *et al.*[13] found that, among 540 patients, two of the brachytherapy group had grades 3-4 complications, and three of the teletherapy group had grades 3-4 complications. The PORTEC study[16] described 2% of grades 3-4 toxicity in the teletherapy group, with 354 women and the GOG 99[17]described 5% of grades 3-4 toxicity in the group of 190 women subjected to external radiotherapy.

In the present study, grades 3-5 toxicity was 27% in the teletherapy group, markedly higher than in the other groups, even higher than in the literature. The patients who did not receive radiotherapy had the best prognostic factors, and therefore had no postoperative treatment. The teletherapy group had worse prognostic factors, what induced more aggressive intervention to these patients. This historic comparison is very important, because it shows progressive changes, during time, in the adjuvant radiotherapy magnitude, always based in retrospectives studies. In our series, the more aggressive treatment led to a worse outcome, due the higher toxicity of teletherapy, therefore, contraindicated for these patients. There was no significant statistical relation between lymphadenectomy and higher toxicity, in this series.

Several authors agree on the adjuvant radiotherapy indication for the old FIGO stage IB and grade 3 subgroup, giving preference to teletherapy in these cases[10,15-19]. Despite the prevalence of this disease, there is no consensus for the adjuvance of cancer of the endometrium stage IA, histological grades 1 and 2 patients, due to the lack of randomized studies. The findings of the PORTEC[16] and GOG 99[17] studies showed that most recurrences of initial tumors were limited to vagina, which, added to low toxicity of this treatment, encourages the use of adjuvant brachytherapy in these cases, but still without strong evidence in the literature.

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