Chapter 2

Postoperative radiation therapy improves prognosis in patients with adverse risk factors in localized, early stage cervical cancer; a retrospective comparative study.

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Int J Gynecol Cancer 2006; 16:1112-1118
Abstract

**Objective:** To assess the role of postoperative radiotherapy for early stage cervical carcinoma with risk factors other than positive nodes, parametrial invasion or positive margins, and to compare outcomes using the Leiden University Medical Centre (LUMC) modification of the Gynecologic Oncology Group (GOG) system with the GOG prognostic scoring system itself.

**Methods:** Between January 1984 and April 2005, 402 patients with early stage cervical cancer underwent radical hysterectomy. Fifty-one patients (13%) had 2 of the 3 risk factors; pathological tumour size ($\geq 40\text{mm}$), invasion ($\geq 15\text{ mm}$) and capillary lymphatic space involvement and were identified as the so-called High Risk group (HR group). We compared 34 patients who received radiotherapy based on the LUMC risk profile (67%) with 17 who did not (33%). The GOG score was calculated as well. We compared the GOG scores within the LUMC risk groups: HR+ (2 out of 3 risk-factors) and HR- (less than 2 out of 3 risk-factors).

**Results:** Differences in 5-year Cancer Specific Survival (CSS) and 5-year Disease Free Survival (DFS) between the HR group treated with (86%; 85%) and without radiotherapy (57%; 43%) were statistically significant. The LUMC criteria did not significantly differ from the GOG risk profile, concerning recurrence, CSS and DFS.

**Conclusions:** High-risk patients benefit from adjuvant radiotherapy. The LUMC modification of the GOG system seems to be simpler, has a slightly higher threshold for the indication for radiotherapy, but without a difference in outcome.
Introduction

The treatment for women with early stage cervical cancer (FIGO I-IIa) (1) can either be a radical hysterectomy with pelvic lymphadenectomy (RHL) or radiotherapy. When RHL is performed and adverse risk factors are present, such as lymph node involvement, parametrial invasion and positive surgical margins, postoperative radiotherapy is indicated (2-12). However, within the group of recurrences, 50% of these patients are without these risk factors (13-16). Several studies have suggested that patients with disease confined to the cervix but with certain other primary tumour related risk factors might also benefit from postoperative radiotherapy (3;17-20). In a study performed by the Gynecologic Oncology Group (GOG), Delgado et al. identified capillary lymphatic space involvement (CLS), clinical tumour size and depth of tumour invasion into the cervical stroma (DI) as independent prognostic variables. A GOG score >120 was correlated with a 41% recurrence rate (3). In a randomised GOG trial, Sedlis et al. used the GOG scoring system and combined the risk factors large tumour size, deep (greater than one third) stromal invasion and the presence of CLS. The authors reported a 44% reduction of the risk of recurrence after adjuvant radiotherapy when a combination of these risk factors was present compared without radiotherapy (12).

Before 1997, patients in our centre received adjuvant radiotherapy if lymph node involvement, parametrial invasion or positive surgical margins were found. In 1997 we extended the indication for postoperative radiotherapy, using a modification of the GOG scoring system. Patients with at least 2 of the following 3 risk factors received postoperative radiotherapy: pathological tumour size (≥40mm), depth of invasion (≥ 15 mm) and CLS. The choice for the definition of these risk factors was based on the results from the literature (3;21;22) and on a retrospective analysis of our own treatment results, indicating that depth of invasion ≥ 15mm was an independent prognostic risk factor (23). The aim of the present study was to assess treatment outcome of patients with early stage cervical carcinoma (FIGO I-IIa) (1) without lymph node involvement, parametrial invasion or positive surgical margins, but with the presence of these adverse risk factors. We compared the outcome of patients who received adjuvant radiotherapy on the basis of adverse tumour factors mentioned above with patients with a similar risk profile treated before 1997 who did not receive radiotherapy. Finally, we compared prognosis of patients using our criteria for giving adjuvant radiotherapy (Leiden University Medical Centre (LUMC) risk profile) with those of the GOG prognostic scoring system (GOG risk score (RS)) (3).

Material and Methods

Study group

Between January 1984 and April 2005, 643 patients with stage I-IIa cervical carcinoma were treated in our centre (LUMC) with a RHL. Relevant clinical and pathological parameters of this group of pa-
Postoperative radiation therapy in patients with adverse risk factors

Patients were prospectively collected in a database. Patients with lymph node involvement, parametrial invasion or positive surgical margins were excluded from this study (n=232). One patient received preoperative radiotherapy, 5 patients received preoperative chemotherapy and 3 patients postoperative chemotherapy; they were also excluded from the study.

LUMC risk profile
For the first analysis we selected from the remaining 402 patients the women with at least 2 of the 3 following risk factors: pathological tumour size ≥40mm, depth of invasion ≥15 mm and CLS. Fifty-one (13%) patients met these criteria and were identified as the so-called High Risk group (HR group). Among these 51 patients we compared the prognosis of those patients who received adjuvant radiotherapy (after 1997) with those who did not (before 1997 or protocol violation after 1997). Reasons for protocol violation for not receiving radiotherapy after 1997 were refusal of the patient (n=3) or complicating comorbidity (n=3).

GOG risk score
For the second analysis we used the GOG risk score (RS) (3). A GOG score was calculated for each of the 402 patients by multiplying the 3 relative risk scores (RR) associated with clinical tumour size, depth of tumour penetration and presence or absence of CLS. The GOG used the cervical tumour regression coefficient for the superficial, middle and deep penetration of the tumour (3). Because we used the infiltration depth in millimetres, we took the mean RR of the superficial, middle and deep penetration to calculate the RR for depth of tumour penetration. Furthermore we used the pathological tumour size instead of the clinical tumour size. We could not calculate the RS for 41 (10%) patients because of missing data such as exact depth of invasion or tumour size or information from referring hospitals (conisation and colposcopy). Fourteen patients would receive radiotherapy according to the LUMC RS as well as according to the GOG score, but did not. Nine patients would not receive radiotherapy according to both scorings systems, but they did. These 23 patients were excluded from the analysis, because we were interested in the differences between the 2 scorings systems. A total of 338 patients was left. We divided the patients into 2 groups: RS≤120 and RS>120 and compared the prognosis of these patients with the prognosis of the patients stratified according to our own risk system (LUMC risk profile): the group with 2 out of 3 risk factors present who received adjuvant radiotherapy (HR+) and the group without 2 out of 3 risk factors present who did not receive adjuvant radiotherapy (HR-).

Staging and pathology
Preoperative staging was performed according to the guidelines of the International Federation of Gynaecology and Obstetrics (FIGO) (1). The following characteristics from the pathology slides were documented: tumour size, histologic tumour type and depth of invasion. When no residual tumour was found in the radical hysterectomy specimen, presurgical data from conization or biopsies were
used. The depth of invasion was measured from the most superficial epithelial-stromal interface of the adjacent intra-epithelial process to the lower limits of invasion (24). Capillary lymphatic space involvement (CLS) was considered positive when neoplastic cells were seen within endothelium-lined spaces. Central recurrences were defined as those involving vagina, bladder or rectum. Regional recurrences were those involving the pelvic sidewall but remained confined to the pelvis and distant recurrences were those with disease outside the pelvis with or without pelvic involvement.

Radiotherapy

External beam radiotherapy was administered to the pelvis using a four-field box technique. Patients were treated with 10 MV photons from a linear accelerator to a total dose of 46 Gy in 2 Gy fractions, specified at the isocentre. A brachytherapy boost was given to the vaginal vault in case of extensive CLS (68% of the patients), using vaginal colpostats, 15 Gy low dose rate or equivalent dose, prescribed at 5 mm from the vaginal mucosa.

Survival analysis

The follow-up was closed on April 2005 and ranged for the 402 patients from 0 to 223 months. The mean duration of follow-up was 60 months. The mean and median duration of follow-up for the 51 HR patients was 54 and 40 months, respectively; with adjuvant radiotherapy 50 and 38 months and without radiotherapy 59 and 58 months, respectively. The disease free survival (DFS) was defined as the time from RHL to cytologically or histologically proven evidence of recurrent disease or date last seen. Cancer specific survival (CSS) was defined as the time from date of operation to death by tumour or date last seen. Survival curves were made using the Kaplan-Meier method (25). The difference in DFS and CSS by treatment regimen was evaluated using the log-rank test (25;26). The chi-square test was used to calculate the relative risk and a p-value <0.05 was considered as statistically significant.

Results

High-risk patients according to LUMC risk profile

Fifty-one (13%) patients met the LUMC criteria for postoperative radiotherapy. The clinical and histological characteristics of the HR patients who were treated with (n=34, 67%; after 1997) and without postoperative radiotherapy (n=17, 33%; before 1997 or protocol violation after 1997) are listed in Table 1. Median age was 44 and 42 years for the patients with and without radiotherapy respectively. Apart from the number of deep infiltrating tumours (more frequent in the irradiated group), the various characteristics of the 2 groups were similar.

Recurrence of disease was diagnosed in 11 of these 51 (22%) patients. Of these 11 patients, 8 died of disease (Table 2 and 3). A significantly larger percentage of the HR patients who did not receive
adjuvant radiotherapy had recurrence of disease, with a RR of 0.29 (95% confidence interval 0.1-0.8, p=0.02) (Table 2). Central recurrences were only diagnosed in patients who did not receive adjuvant radiotherapy (Table 3). The median time from surgery to recurrence and from recurrence to death was 15 and 12 months respectively for the total group. Two of the 51 patients died because of other reasons: one because of a psoasabces and diverticulitis and the other because of cardiac failure. The 5-year CSS and DFS of the entire HR group of 51 patients was 74% and 69%, respectively. The 5-year CSS and DFS were 86% and 85% respectively, among the patients treated with adjuvant radiotherapy (n=34) in contrast to the patients without adjuvant radiotherapy (n=17), who had a 5-year CSS and DFS
of 57% and 43%, respectively (Fig. 1A, B). The differences in CSS and DFS between the 2 groups were statistically significant (p=0.013 and p=0.006, respectively).

Comparison of the GOG risk score and LUMC risk profile

Table 4 shows the comparison of the GOG and LUMC risk assessment in the total of 338 patients. In 322 of 338 patients (95%) there was agreement in allocated high-risk profile in the LUMC and the GOG system. In 16 patients (5%) there was no agreement and in all these cases the patients had a high RS according to the GOG system, but not according to the LUMC assessment. Because the threshold to give

<table>
<thead>
<tr>
<th>Recurrence HR group</th>
<th>Radiotherapy n(%)</th>
<th>No radiotherapy n(%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>4(12)</td>
<td>7(41)</td>
<td>11(22)</td>
</tr>
<tr>
<td>No</td>
<td>30(88)</td>
<td>10(59)</td>
<td>40(78)</td>
</tr>
<tr>
<td>Total</td>
<td>34(67)</td>
<td>17(33)</td>
<td>51(100)</td>
</tr>
</tbody>
</table>

Table 2. Number and percentage of recurrence of disease in the HR group with and without radiotherapy.

<table>
<thead>
<tr>
<th>Radiotherapy</th>
<th>Months to recurrence</th>
<th>Site of recurrence</th>
<th>Survival after recurrence (months)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>5</td>
<td>distant</td>
<td>7</td>
<td>DOD</td>
</tr>
<tr>
<td>Yes</td>
<td>14</td>
<td>regional</td>
<td>14</td>
<td>NED</td>
</tr>
<tr>
<td>Yes</td>
<td>20</td>
<td>regional</td>
<td>0</td>
<td>ALD</td>
</tr>
<tr>
<td>Yes</td>
<td>31</td>
<td>distant</td>
<td>34</td>
<td>DOD</td>
</tr>
<tr>
<td>No</td>
<td>7</td>
<td>central</td>
<td>8</td>
<td>DOD</td>
</tr>
<tr>
<td>No</td>
<td>7</td>
<td>central+regional</td>
<td>213</td>
<td>NED</td>
</tr>
<tr>
<td>No</td>
<td>10</td>
<td>central</td>
<td>10</td>
<td>DOD</td>
</tr>
<tr>
<td>No</td>
<td>15</td>
<td>regional</td>
<td>14</td>
<td>DOD</td>
</tr>
<tr>
<td>No</td>
<td>25</td>
<td>central+regional</td>
<td>32</td>
<td>DOD</td>
</tr>
<tr>
<td>No</td>
<td>37</td>
<td>central+regional</td>
<td>32</td>
<td>DOD</td>
</tr>
<tr>
<td>No</td>
<td>51</td>
<td>distant</td>
<td>9</td>
<td>DOD</td>
</tr>
</tbody>
</table>

Table 3. HR patients with recurrent cervical carcinoma. DOD, dead of disease; NED, no evidence of disease; ALD, alive with disease.

Comparison of the GOG risk score and LUMC risk profile

Table 4 shows the comparison of the GOG and LUMC risk assessment in the total of 338 patients. In 322 of 338 patients (95%) there was agreement in allocated high-risk profile in the LUMC and the GOG system. In 16 patients (5%) there was no agreement and in all these cases the patients had a high RS according to the GOG system, but not according to the LUMC assessment. Because the threshold to give

<table>
<thead>
<tr>
<th>RS&lt;120 (GOG) (n)</th>
<th>HR- (LUMC) (n)</th>
<th>HR+ (LUMC) (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>288</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>RS&gt;120 (GOG) (n)</td>
<td>16</td>
<td>34</td>
</tr>
<tr>
<td>Total (n)</td>
<td>304</td>
<td>34</td>
</tr>
</tbody>
</table>

Table 4. Table of the number of patients; GOG prognostic scoring system versus LUMC system. HR; high risk group, RS: GOG risk score.
adjunct radiotherapy was lower using the GOG prognostic scoring system, we determined if there would be a difference in CCS and DFS when the GOG RS was used instead of the LUMC risk profile. To answer this question the HR + group (high risk group, n=34) was compared with the HR- group (no high risk group, n=16). The 2 groups were treated according to the LUMC system; the HR+ group did receive radiotherapy and the HR- group did not. Both groups had a RS>120 (GOG system).

Eight of the 50 patients (16%) had recurrence of the disease, four patients in each group (HR+: 12%, HR-: 25%). There was no statistically significant difference in recurrence between these 2 groups (RR 0.5, 95% confidence interval 0.13-1.7, p=0.23).

For the 34 high-risk patients (HR+; RS>120) who received radiotherapy the median time from therapy to recurrence was 18 months, from recurrence to death 20 months. For the 16 patients (HR-; RS>120) treated without radiotherapy time to recurrence was 20 months, from recurrence to death 39 months. One of the 50 patients died because of a psoas abscess and diverticulitis.

The 5-year CSS and DFS of the entire group of 50 patients (HR+ and HR- groups with a RS>120) were 88 and 79%, respectively. The 5-year CSS and DFS were 86% and 85% among the HR + group (n=34), in contrast to 92% and 62% for the HR- group (n=16) (Fig. 2 A, B). These differences were however, not statistically significant (p=0.444 and p=0.212, respectively).

Figure 1. Survival (A) and disease free survival (B) of the HR group with adjuvant radiotherapy (n=34) and the HR group without radiotherapy (n=17).
Postoperative radiation therapy in patients with adverse risk factors

Chapter 2

Discussion

The role of postoperative radiotherapy was evaluated for patients with early stage cervical carcinoma with tumour related risk factors, other than positive nodes, parametrial invasion or positive margins. The current study indicated that the high risk group according to the LUMC risk profile, characterized by at least 2 of the 3 risk factors, significantly benefitted from postoperative radiotherapy. We found that a significantly larger percentage (41 vs 12%, p=0.02) of the HR group who did not receive radiotherapy, had recurrence of disease. Central recurrence only appeared in the latter group. The differences in CSS and DFS between the HR group with adjuvant radiotherapy (86%; 85%) and HR group without adjuvant radiotherapy (57%; 43%) were statistically significant. The fact that the patients who did receive postoperative radiotherapy might represent a higher risk group as far as the percentage of deep infiltrating tumours is concerned, underlines this conclusion. Furthermore, this study showed that the LUMC modification of the GOG prognostic scoring system did not significantly differ from the GOG prognostic scoring system itself, with regard to risk of recurrence, CSS and DFS.

The strength of the current study is the fact that a prospective database and a consecutive series of patients were used. However, the observations are based on limited numbers of patients. Our results concerning the benefit of radiotherapy for the HR group are according to the literature. Delgado et al. found CLS, clinical tumour size and DI to be the parameters best predicting prognosis in patients with early stage cervical cancer with negative lymph nodes. Using the GOG prognostic scoring system, they found that in patients with a combination of these risk factors, but with negative nodes, the 3-year risk of recurrence could be as high as 41% (3). In a randomised study, Sedlis et al. used

Figure 2. Survival (A) and disease free survival (B) of the HR+ and HR- group and both with a RS>120.

(HR-, RS>120, RT-: Less than 2 of the 3 risk factors positive, a GOG risk score>120 and no adjuvant radiotherapy (RT))

(HR+, RS>120, RT+: At least 2 of the 3 risk factors positive, GOG risk score>120 and adjuvant radiotherapy (RT))
Postoperative radiation therapy in patients with adverse risk factors

a modification of the GOG scoring system and included 277 patients with stage Ib cervical carcinoma with at least 2 out of 3 risk factors: CLS, large tumour size and DI (greater than one third). The results of this study showed that the risk of recurrence was significantly reduced by 44% (p=0.02) in patients treated with postoperative radiotherapy (12). Furthermore, a recent study by Rushdan et al. reported that postoperative radiotherapy given in patients with a high risk score, significantly improved their 5-year recurrence rate and disease-free survival (27). Similar results were also reported by other investigators (7;13).

However, in the retrospective analysis by Van der Velden et al. no survival benefit was found using adjuvant radiotherapy for risk factors other than positive nodes, parametrial extension and positive margins. They reported that the variant of RHL could be an explanation for the observed difference between this study and literature data. Van der Velden et al. used the Wertheim/Okabayashi variant of the RHL, with a more radical removal especially of the lower parametrial and paracolpal tissues compared to Wertheim/Meigs procedure (28). Because of the expected higher morbidity rate of the Wertheim/Okabayashi procedure, we perform the Wertheim/Meigs variant (29).

The cited studies used the GOG prognostic scoring system or a modification of it to decide on the indication for radiotherapy. To calculate a GOG score for an individual patient, one has to multiply 3 relative risk scores associated with exact tumour size, DI related to the specific part of the uterine wall, and the presence or absence of CLS. This requires various pathology details. All 3 details were not always available in our group of patients and therefore we could not calculate the GOG risk score in 10% of the cases.

Furthermore, the LUMC risk profile is simpler and more straightforward than the GOG prognostic scoring system and even simpler than the modification of Sedlis et al.(12). In the current study, there was 95% (n=322) agreement in allocation of a high-risk profile to the patients for the LUMC and the GOG system. According to the GOG system, 5% (n=16) of the LUMC low risk patients would have had an indication for radiotherapy. This difference did not affect the prognosis of these patients in any detectable way; there was no significant difference in recurrence of disease, CSS and DFS, although statistical significance might not have been reached because of the small number of patients.

The risk of late side effects after adjuvant radiotherapy could be an argument against adjuvant radiotherapy in absence of the major risk factors lymph node metastases, positive margins or parametrial involvement. However, in a recent study of our own data we found that adjuvant radiotherapy did not significantly increase the risk of bladder dysfunction, bowel symptoms, lymphedema and sexual function after 2 years follow-up (30).

It is concluded that, despite the relatively limited numbers of patients analyzed, the current study confirms that high-risk patients significantly benefit from adjuvant radiotherapy. Moreover, this study compared in a prospective way a modification of the GOG RS to the GOG prognostic scoring system itself. Furthermore, we found that the LUMC risk profile is simpler and more straightforward in use, has a slightly higher threshold to define patients as high risk who need adjuvant radiotherapy as compared to the GOG prognostic scoring system, but without compromising their prognosis.
References


Rushdan MN, Tay EH, Khoo-Tan HS, Lee KM, Low IH, Ho TH et al. Tailoring the field and indication of adjuvant pelvic radiation for patients with FIGO stage Ib lymph nodes-negative


