High-dose weekly fractionation radiotherapy in advanced cancer of the uterine cervix

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Summary

A trial comparing two different radiotherapy techniques and schedules in the treatment of 83 patients with advanced cancer of the uterine cervix (stage IIIB) employing external irradiation alone is described. The one technique, used routinely in this department, employed a conventional daily fractionation schedule while the other used a high-dose weekly fractionation regimen. The techniques are described. The aim of the trial was to compare the efficacy and morbidity of these two methods of treatment.

Dose distribution curves in cross-section and mid-sagittal planes are shown and calculations or equivalent doses at various selected points using Ellis’s nominal single-dose formula are tabulated. The 2-year survival figures were 33% for the daily fractionation technique and 22% for the weekly regimen. Serious late complication rates were 6% for the daily regimen and 22% for the weekly schedule. These differences are not statistically significant. Late complication rates in the weekly fractionation regimen appeared to be lower than figures quoted by other authors. Local control within the irradiated volume was better in the group treated by the daily fractionation method.

Advanced squamous carcinoma of the cervix (stage IIIB) carries an overall poor prognosis, with 5-year survival varying between 16% and 30%. In our department, treatment for the advanced stages where an intracavitary isotope could not be applied was by external irradiation alone, with bi-axial and anterior arcs (described later). The fractionation schedule consisted of 29 daily fractions to the pelvis to a total dose of 60 Gy. The volume around the cervix, which included point A, received a slightly higher dose of 65 Gy. The 2-year survival figures were in the range of 20 - 25%.

A simple 360° rotation technique with daily fractionation was introduced and a randomized trial instituted to compare this method of treatment with our routine technique. At the end of the trial the decision was to retain the bi-axial technique for radical treatment because the results were superior (N. G. de Moor — unpublished results).

However, for stage IV carcinoma of the cervix the simple 360° rotation technique and weekly fractionation was introduced. Four weekly doses of 7.5 Gy at the axis of rotation were given to a total of 30 Gy. The 2-year survival figure was 15%.

For various reasons, including consideration of factors such as patient compliance, lack of hospital beds and machine time, a decision was made to introduce weekly fractionation as a radical treatment of stage IIIB carcinoma of the cervix in those patients in whom intracavitary caesium could not be applied. It was hoped that the schedule using a high dose per fraction and a longer time interval between fractions would be more efficient in sterilizing these large tumours; the latter probably contain a high proportion of hypoxic cells and in addition may re-oxygenate poorly between daily fractions. The larger time interval between fractions may lead to better re-oxygenation. The overall treatment time would be decreased from 6 weeks to 4 weeks.

A randomized prospective trial was started in January 1977 and closed in December 1978. Patients were randomized into two groups. Patients in group 1 were treated by our routine daily fractionation regimen using the bi-axial technique and patients in group 2 were treated 5 times by a weekly fractionation schedule using the 360° rotation technique. This technique is extremely attractive because it is simple and considerably reduces patient set-up time. It was hoped that by combining this technique with a high-dose-per-fraction regimen acceptable results would be achieved.

Patients and methods

The patients selected were those with advanced carcinoma of the cervix (stage IIIB) in whom an afterloader for intracavitary caesium could not be introduced. Eighty-three patients were randomized into the two groups, 39 in group 1 and 44 in group 2. The age distribution in both groups was similar (Table I) and no patient older than 70 years was included in the trial.

A similar proportion of patients in both groups had abnormal intravenous pyelograms — 51% in group 1 and 49% in group 2. This factor adversely affects prognosis. No patients with blood urea and serum creatinine values greater than 30% above the upper limits of normal were included in the trial. Staging was performed by a gynaecologist and radiotherapist at our gynaecology oncology clinic.

Irradiation technique

Group I

In this group the technique consisted of irradiation through a left and right 180° arc, each centred on the midcoronal plane 4 cm lateral to the midsagittal plane. The superior border passed through the middle of the 5th lumbar vertebra. The inferior border passed through or below the lower borders of the obturator foramina, depending on the extent of vaginal involvement. Field sizes were of the order of 8 cm wide x 16 cm long.
TABLE I. AGE DISTRIBUTION

<table>
<thead>
<tr>
<th>Age group (yrs)</th>
<th>Group 1 — daily</th>
<th>Group 2 — weekly</th>
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<tbody>
<tr>
<td>10 - 19</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>20 - 29</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30 - 39</td>
<td>3</td>
<td>7.7</td>
</tr>
<tr>
<td>40 - 49</td>
<td>10</td>
<td>25.6</td>
</tr>
<tr>
<td>50 - 59</td>
<td>12</td>
<td>30.8</td>
</tr>
<tr>
<td>60 - 69</td>
<td>10</td>
<td>25.6</td>
</tr>
<tr>
<td>Total No.</td>
<td>39</td>
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</table>

Twenty-five daily doses of 1.8 Gy were given to these points, to a total of 45 Gy. In addition an anterior central 75° arc was added as a central booster, giving 10 Gy in 4 weekly doses. The dose distribution in the central cross-section (contour level) is shown in Fig. 1 and in the sagittal plane in Fig. 2. The isodose line of 60% received 60 Gy.

Group 2

In this group simple 360° rotation irradiation was used. The intersection in the pelvis of the midcoronal and midsagittal planes was taken as the axis of rotation. Superior and inferior borders were chosen as for group 1. Field sizes were of the order of 14 cm wide x 16 cm long. Five weekly doses of 7.5 Gy were given to the centre to a total of 37.5 Gy. Fig. 3 shows the dose distribution at the central contour level and Fig. 4 shows the distribution in the sagittal plane. The 100% isodose line receives 37.5 Gy.

Both treatments were given on the same cobalt-60 machine.

Results

Table II compares the calculated total doses received at various points in the pelvis. These points were selected at various sites on the dose distribution curves (Figs 1 - 4); actual doses were calculated from the values of the percentage isodose lines passing through these points. The total dose from the weekly regimen was converted to the equivalent total dose on our daily regimen by using the Ellis nominal single-dose (NSD) formula for normal tissue. Thus, in group 1 the rectum received 50 Gy and the sigmoid 70 Gy but in group 2 these points received 61.2 Gy and 60 Gy respectively.

TABLE II. EQUIVALENT RELATIVE DOSE TO NORMAL TISSUE (cGy; NORMALIZED TO DAILY FRACTIONS)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Daily treatment (group 1)</th>
<th>Weekly treatment (group 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>6000</td>
<td>6180</td>
</tr>
<tr>
<td>Distal rectum</td>
<td>6000</td>
<td>6000</td>
</tr>
<tr>
<td>Proximal rectum</td>
<td>5000</td>
<td>6120</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>7000</td>
<td>6000</td>
</tr>
</tbody>
</table>

ANTERIOR

Fig. 1. Lateral arc and anterior booster technique, stage IIIB cervical cancer — the dose distribution at transverse contour level (daily fractionation).

ANTERIOR

Fig. 2. Lateral arc and anterior booster technique, stage IIIB cervical cancer — the dose distribution in the sagittal plane (daily fractionation).

ANTERIOR

Fig. 3. 360° rotation technique, stage IIIB cervical cancer — the dose distribution at contour level (weekly fractionation).

ANTERIOR

Fig. 4. 360° rotation technique, stage IIIB cervical cancer — the dose distribution in the sagittal plane (weekly fractionation).
Fig. 5. Actuarial survival rates. Number on graph indicates number of patients at risk during the next 5-month interval. Daily fractionation, group 1 ——; weekly fractionation, group 2 —— ● ——.

Fig. 5 shows the actuarial survival curves drawn for both groups. There is no significant statistical difference between the two results (log rank test).

Table III outlines the sites of tumour recurrence or treatment failure. These findings are based on clinical examination, special investigations, biopsies, surgery for complications and the triad of signs for regional recurrence. No autopsies were performed since most patients died at home and relatives refused to give permission for autopsy. Sites of recurrence were established in 56 patients, 26 in group 1 and 30 in group 2. This information could not be ascertained in 17 deceased patients. Figures quoted under locoregional control refer to control within the irradiated volume. 5,6

If the 10 survivors are included (6 in group 1 and 4 in group 2), local control was obtained in 16 out of 32 in group 1 and 6 out of 34 in group 2. This difference is statistically significant ($P < 0.01$).

### Morbidity

There was no difference between the two groups as regards the incidence of acute reactions such as diarrhoea, dysuria and skin lesions. When they occurred these reactions seldom required a discontinuation of treatment.

Table IV gives the number of patients who suffered late irradiation complications requiring surgery for correction. In addition, there were 3 patients in group 1 and 4 in group 2 with proctitis who responded completely to conservative management.

In every case clinical investigations and biopsies were performed to exclude tumour recurrence; these late complications were not seen before 6 months after the start of therapy. Therefore, in calculating late complication rates only patients who had survived 6 months or longer were included in the calculations and not all the patients in the groups, as this might have given a falsely lower complication rate.

The 33 patients in group 1 and 32 in group 2 who survived for periods of 6 months or longer are listed in Table IV. There was a complication rate of 6% in group 1 and 22% in group 2, but this difference is not statistically significant.

### Discussion

Treatment of carcinoma of the cervix by teletherapy alone has been described by several authors. 7,8 Their results were encouraging both with respect to tumour control and low complication rates. External irradiation is the only proven method capable of delivering the effective homogeneous dose to large volumes required in the treatment of stage IIIB carcinoma of the cervix.

External irradiation alone is probably the treatment of choice in the advanced stage IIIB case with bilateral pelvic wall involvement. Based on these considerations, the techniques using external irradiation alone and daily fractionation were introduced in our department.

For reasons previously discussed, weekly fractionation would offer considerable benefit to both the patients and the department if the results with this form of therapy were comparable to those achieved with daily fractionation. However, a number of problems arose in attempting to convert a satisfactory radical daily fractionation regimen to an equivalent weekly high-dose fractionation schedule. These difficulties relate to the calculation of the dose per fraction, the number of fractions (or total dose), and the time interval between fractions.

Mathematical formulae may be applied to achieve the conversion of one dosage regimen to another, so that the total dose does not exceed the tolerance of normal tissue or organs at risk. The Ellis NSD formula has been most frequently used for this purpose. In this study, the NSD value was 1760. This figure could be expected to indicate that the proposed fractionation scheme would not result in a radiation dose which exceeded normal tissue tolerance. However, it should be emphasized that this figure may not correlate with an equivalent probability of tumour control, particularly when it is considered that the formula is based on the radiation tolerance of normal tissue, which may differ from the sensitivity of tumour tissue.

The results of the present study indicated that the daily and weekly fractionation schedules gave statistically equivalent 2-year survival rates of 33% and 22% respectively. However, the

### Table III. Number of Patients with Tumour Recurrence

<table>
<thead>
<tr>
<th></th>
<th>Total No. assessed</th>
<th>C</th>
<th>R</th>
<th>C+R</th>
<th>C+M</th>
<th>M+R</th>
<th>C+M+R</th>
<th>M</th>
<th>No. with locoregional control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (daily)</td>
<td>26</td>
<td>7</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Group 2 (weekly)</td>
<td>30</td>
<td>14</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

*Where information was available. C = central (cervix and paracervical); R = regional (pelvic wall and iliac nodes); M = metastases (extrapelvic nodes and blood spread).
daily schedule resulted in satisfactory local tumour control in 16 out of 32 patients, a figure significantly greater than that for the weekly schedule which was effective in only 6 out of 34 patients. Furthermore, the weekly regimen caused more late complications than did daily radiation therapy.

While this difference was not statistically significant at $P < 0.05$, the null hypothesis that these complication rates were equivalent could be rejected at $P = 0.07$. It should be noted that other authors have also questioned the validity of the Ellis NSD formula in predicting the late complication rate when high-dose fractions are used.2,6

In conclusion, therefore, daily and weekly fractionation regimens give similar 2-year survival rates for treatment of advanced carcinoma of the cervix, but better local control is achieved with the daily fractionation bi-axial technique. These factors together with the concern that weekly fractionation may result in a higher complication rate suggest that daily fractionation should remain the preferred treatment, particularly as local control of pelvic disease is a primary objective in the treatment of advanced carcinoma of the cervix. However, improved results with the weekly regimen may be obtained by improving the treatment plan, making this form of therapy an acceptable alternative.

REFERENCES


Treatment of progressive ovarian cancer with cis-platinum and doxorubicin

B. BLOCH

Summary

Thirty-two patients with progressive ovarian carcinoma which had not responded to primary therapy were treated with cis-diaminedichloroplatinum (II) (CDDP) (50 mg/m²) and doxorubicin (50 mg/m²) on day 1 as second-line chemotherapy. An overall response rate of 28% was achieved, the mean duration of response being 5 months. These results are not significantly different from results achieved with other agents used in similar circumstances, but in the light of recent experience it is suggested that this combination warrants a trial as first-line therapy.

Various chemotherapeutic agents, alone and in combination, are at present accepted as the treatments of choice for stage III and IV ovarian cancer, but because 60% of patients present with advanced disease the search for more effective single agents or combinations which will lessen morbidity and decrease mortality rates continues.

Response rates produced by alkylating agents vary between 40% and 60% and response rates produced by combinations of cyclophosphamide, hexamethylmelamine, doxorubicin and cis-diaminedichloroplatinum (CDDP) between 0% and 63%. CDDP has been reported as producing response rates of 26.5%4 31.5%,5 34%6 and 70%7 in varying doses and combination schedules when used as primary, secondary and tertiary therapy. CDDP in combination with doxorubicin has recently been reported as producing a response rate of 80%8 when used as first-line therapy.

We report on the efficacy of a combination of CDDP and doxorubicin administered every 4 weeks as second-line chemotherapy in patients with stage II, III and IV ovarian cancer which had not responded to other forms of therapy.

Patients and methods

Thirty-two patients with tumours which had progressed on other forms of therapy and who had objectively evaluable disease were entered into the study.

Evaluation of the patients performed before therapy commenced included a full blood count, 12/60-channel analysis including determination of blood urea nitrogen and serum creatinine values, liver function tests, a creatinine clearance test, chest radiography, electrocardiography and hepatic ultrasound examination. Thereafter, the full blood count, 12/60-channel