The management of advanced and recurrent carcinoma of the cervix

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INTRODUCTION It is an unfortunate fact that stage IIIB, III and IV carcinoma of the cervix is still frequently seen, especially in patients of lower socio-economic status. The very people who need PAP smears the most, get it done the least often. There is also a tardiness from the side of Government in many instances to support large-scale screening programs. WHO recommendations suggest the first screening should take place at 35 years of age, but in fact the damage is done to the transitional zone by the papilloma virus and possibly by trauma, long before that age. Many people in the lower socio-economic strata participate in sex shortly after the menarche, so that there is already ten years that the virus had time to transform the cells, and even at the age of 25 then, many females are already saddled with CIN II or III, or even invasive carcinoma. Education and screening, should in the opinion of the members of our Combined Clinic in Tygerberg, be started at an early age, certainly no later than age 25.

THE MANAGEMENT OF ADVANCED CARCINOMA OF THE CERVIX

The best management would be prevention. However, when faced with an advanced carcinoma, the treatment is mainly radiotherapeutic.

STAGING Proper staging in a combined clinic is very important, and an adequate work-up is essential to exclude metastatic disease. This includes a bone scan, cystoscopy, chest x-ray, sonar of the liver, intravenous pyelogram to exclude hydronephrosis, and blood tests to test the haemoglobin levels and other relevant parameters, as well as kidney and liver functions. Patients with hydronephrosis seldom fare well, but if the patients are of good performance status, with adequate haemoglobin levels, it is our policy to treat and if all goes well, to persist to a radical dose.

Planning should be done by means of a CT scan wherever possible, as it is important to encompass all detectable disease properly. The fault that is commonly made by simple simulation, is that the extent of the disease posteriorly and lateral to the rectum is underestimated. Similarly, disease can often be seen on CT planning to extend anteriorly and make a bulge into the bladder, even if the bladder is not infiltrated. The superior limit of the disease is difficult to define, and the entire fundus should be included. Sometimes a myoma can be ignored from the treatment volume if the latter is calcified, which may signal a benign confounding factor. It is very important to make exact sketches of the extent of the tumour and to carefully note the extent of extension into the vagina especially to the middle or lower third, in order to ensure proper coverage of the disease. The extent of parametrical involvement must be recorded carefully prior to planning. Unilateral pelvic extension, especially to the right parametrium, may prompt a note on the prescription form to consider additional irradiation to the affected side, especially where the response is not adequate by the time the external beam radiotherapy is completed.

The patient should be re-examined on the CT scanner bed (which should be flat, like the treatment couch). A tampon, of which the tip has been dipped into a radio-opaque dye, should be used to mark the inferior limit of the tumour. The treatment fields should extend well below this marker for 2 reasons: firstly to anticipate microscopic subepithelial creep, and secondly, because three dimensional reconstruction of isodose curves in the sagittal plane, will show a distinct tendency to “contract” about 1 cm in the sagittal plane.

Wherever possible, the patient should be scanned, and treated with a full bladder. This helps to displace the more sensitive intestine out of the high dose zone.

The upper limit of the field is perhaps of lesser importance than the cervical and parametrical zone; local control is the primary objective. Field lengths are typically about 14 to 16 cm, but where disease comes down low in the vagina, the fields may reach 18 cm or more in length, and to treat such long fields to a high dose is probably to invite serious compli-
cations. Faced with such a situation, the trend should perhaps be to rather cut a centimetre or two off the superior border. The patient should be treated with multiple fields, all treated every day rather than with two parallel opposing fields. We commonly use a fourfield “box” technique. Field shaping is difficult where a large patient load faces a department, but should be attempted or the possibility assessed for each patient.

**BEAM ENERGY** The best dose distributions are obtained with 8-16 MeV photons, depending on the separation (thickness) of the patient. Lower energies should probably be avoided.

**FRACTIONATION** The fraction size should be 1.8 Gy to 2 Gy per fraction, and no larger. The routine at Tygerberg is to use 27 fractions on the whole pelvis to a total dose of 54 Gy in 33 days, supplemented by four doses of 4 Gy to “point A” intracavitary treatment daily, total 16 Gy, to a total dose of 70 Gy at “point A”, giving a total treatment time of 38 days. The intracavitary treatment is by means of an 192Iridium remotely controlled afterloader, the “Gammamed II” from Isotopen Technik Sauerwein.

**INTRACAVITARY THERAPY** It has been shown by Hanks et al. (1) that the intracavitary therapy is crucial to the optimal therapy for late stage disease – especially to control central recurrences. The technique used in our institution is that described by Smit et al. (2-4). This technique briefly, comprises the insertion of an indwelling nylon tube or stent into the uterus on day 33. This tube is inserted under local anaesthesia (a paracervical block with about 10-15 ml of 1% lignocain injected paracervically), or by a brief general anaesthetic. The tube is left in position for advanced carcinoma for 5 days. With practice, four patients can be fitted with tubes per hour. This tube makes it extremely easy to relocate and accurately place the usual intracavitary applicators daily for 4 days with great comfort to the patient. (Four fractions of 4 Gy each delivered to “Point A”).

A Foley’s catheter is cut at the side, the applicator threaded through so that the bulb surrounds the applicator. This gives an unobstructed view of the tube in the uterus, and the bladder and rectum are then displaced away from the high dose zone by water injected into the bulb of a 40 ml Foley’s catheter.

This system allows adequate and flexible irradiation of the fornices, and in fact gives superior irradiation to the parametria compared to the more conventional colpostats, which irradiate the paracolpos mainly, and also delivers an unnecessarily large dose to the vaginal surface, despite the risk of a cold spot on the cervix! For the same AP diameter of the isodose as obtained with colpostats, the sparing of the bladder and rectum are not inferior. With this system, the patient is irradiated with a full (but not overstretched) bladder, which ensures autoprotection of the anterior and lateral walls of the bladder. Superior fractionation, with better radiobiological sparing of the normal, late reacting tissues, is achieved without supernumerary anaesthetics. Careful dosimetry with CT scans with the applicator system in situ showed that the bladder and rectal doses are within acceptable, and reproducible limits (Figure 1a and 1b).

**TOTAL TREATMENT TIME** The time of the treatment is important. The longer the overall treatment time, the worse the prognosis with a highly significant difference between overall treatment times of <6, 6-7.9, 8-9.9 and 10+ weeks (5). Our own overall treatment time is 38 days i.e. <6 weeks. The total treatment time with the above scheme is 38 days, the total TDF 90 (external) plus 40 (intracavitary to point A) so that the total TDF to point A is 130 (6). Chougule et al. (7) showed that for carcinoma of the cervix the TDF and TSD concepts predicted probable tumour response as well as the LQ model. A narrow, 3cm wide “boost” is sometimes give to persistent involvement of, especially the right parametrium (less risk than the left parametrium with the rectosigmoid in the field) The field length for this boost is usually no longer than 8-10 cm, and is given with 8-16 MeV photons by two parallel opposing fields.

With this approach, an actuarial survival rate for stage III carcinoma of 60 per cent, and an absolute 5 year survival of 39.7 per cent was achieved in 732 patients (8). The complication rate was low, 6% for late grade 2-3 cystitis/procititis.

**CHEMOTHERAPY AS SENSITIZERS** Various efforts have been made to improve the 5 year survival of patients with advanced carcinoma of the cervix. The better “complete response rates” achieved with combination chemotherapy appears to be 29 per cent, with a combination of mitomycin-C, vincristine, bleomycin and cisplatinum (in 14 patients), and with doxorubicin and methyl CCNU (31 patients) (9). Smit et al. (10) showed an actuarial survival of 60% (RT alone); 84% (RT+ Cisplatin) and 85% (RT+ Hydrea) in a small controlled study (Figure 1.) confirming findings by Piver et al. (11). Further references on this topic are obtainable in Perez (9). Complications were not
**Table 1. Complications of combined radiation and chemotherapy (10)**

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Cystitis No (%)</th>
<th>Proctitis No (%)</th>
<th>Diarrhoea No (%)</th>
<th>RVF/ VVF</th>
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<tbody>
<tr>
<td>(20 patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>RT + Cisplatin</td>
<td>1 [4.7]</td>
<td>-</td>
<td>3 [14.2]</td>
<td>-</td>
</tr>
<tr>
<td>(21 patients)</td>
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<tr>
<td>(22 patients)</td>
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**LATE COMPLICATIONS**

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Cystitis No (%)</th>
<th>Proctitis No (%)</th>
<th>Diarrhoea No (%)</th>
<th>RVF/ VVF</th>
</tr>
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<tbody>
<tr>
<td>RT alone</td>
<td>-</td>
<td>2 [10]</td>
<td>-</td>
<td>-</td>
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<tr>
<td>(20 patients)</td>
<td></td>
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<td>(21 patients)</td>
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<tr>
<td>RT + Hydrea</td>
<td>1 [4.5]</td>
<td>2 [9.1]</td>
<td>2 [9.1]</td>
<td>-</td>
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<tr>
<td>(22 patients)</td>
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RVF: Retrovaginal fistula  VVF: Vesico-vaginal fistula

Severe (Table 1). Recently, gemcitabine has been identified as an active drug (12).

**MANAGEMENT OF RECURRENT CARCINOMA** This is always a very frustrating, usually debilitating, but not always fatal occurrence. Monaghan (13) is very positive in his approach to recurrent disease. According to this source, survivals with exenteration now reaches 40% to 60% in recently reported large series. This reader is referred to this excellent review of this subject.

An absolute contraindication is distant metastases. Relative contraindications to surgery include spread to the pelvic sidewall, the triad of unilateral leg oedema, sciatic leg pain and unilateral ureopathy is an ominous sign. Obesity and a poor mental orientation by the patient are risk factors.

Survival at 5 years varied from 18 per cent to 61.8 per cent, so that it is obvious that this procedure may offer some hope to a substantial number of otherwise hopeless patients, but the price in morbidity is relatively high.

**REFERENCES**


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12. Goedhals L. (Bleomfioin) Personal communication.