Combined Modality Treatment of Anal Carcinoma

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Key Words. Combined modality treatment · Radiochemotherapy · Anal carcinoma

ABSTRACT

Within the framework of two phase III clinical trials, the superior results of concomitant chemotherapy and radiotherapy in the treatment of patients with locally advanced anal carcinoma were demonstrated. A further phase III clinical trial showed that the role of mitomycin C as part of the concomitant chemotherapy in combination with 5-fluorouracil appeared to be essential in obtaining a higher local control rate.

INTRODUCTION

Combined modality treatment of anal carcinoma was initiated in 1974, when Nigro reported on three patients with anal carcinoma treated with preoperative irradiation with concomitant 5-fluorouracil (5-FU) and mitomycin C [1]. The experience of complete histological remission in the operative specimen led to a treatment strategy of definitive radiochemotherapy, reserving surgery as a salvage procedure for patients with persistent or relapsing tumors [2, 3]. Since then, many nonrandomized studies have been published supporting the therapeutic effect of sphincter-preserving treatment with a combination of radiotherapy with different schedules, dosages, and applications, including brachytherapy with or without concomitant or sequential chemotherapy. In some studies, high toxicity rates were reported, especially in patients treated with the combination of 5-FU and mitomycin C [4-11].

CLINICAL TRIALS

Recently, three randomized trials have been published confirming the treatment of anal carcinoma with radiotherapy and concomitant chemotherapy containing continuous 5-FU and mitomycin C as the gold standard (Table 1).

The European Organisation for Research and Treatment of Cancer (EORTC) trial and the United Kingdom

<table>
<thead>
<tr>
<th>Eligible patients</th>
<th>Radiotherapy</th>
<th>Radiotherapy + 5-FU + MMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>52</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>T1-T2 N0</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>T1-T2 N+</td>
<td>15%</td>
<td>16%</td>
</tr>
<tr>
<td>T3-T4 N0</td>
<td>48%</td>
<td>45%</td>
</tr>
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<td>T3-T4 N+</td>
<td>32%</td>
<td>39%</td>
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UKCCCR

<table>
<thead>
<tr>
<th>Eligible patients</th>
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<th>Radiotherapy + 5-FU + MMC</th>
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</thead>
<tbody>
<tr>
<td>218</td>
<td>213</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>15%</td>
<td>12%</td>
</tr>
<tr>
<td>T2</td>
<td>33%</td>
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<tr>
<td>T3</td>
<td>40%</td>
<td>41%</td>
</tr>
<tr>
<td>T4</td>
<td>11%</td>
<td>13%</td>
</tr>
<tr>
<td>N+</td>
<td>17%</td>
<td>23%</td>
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RTOG/ECOG

<table>
<thead>
<tr>
<th>Eligible patients</th>
<th>Radiotherapy</th>
<th>Radiotherapy + 5-FU</th>
<th>Radiotherapy + 5-FU + MMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>145</td>
<td>146</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>15%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>35%</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>42%</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>8%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>82%</td>
<td>83%</td>
<td></td>
</tr>
<tr>
<td>N+</td>
<td>17%</td>
<td>17%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EORTC = European Organisation for Research and Treatment of Cancer; UKCCCR = United Kingdom Coordinating Committee on Cancer Research; RTOG/ECOG = Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group; MMC = mitomycin C.
Coordinating Committee on Cancer Research (UKCCCR) trial compared radiotherapy alone with radiotherapy and concomitant 5-FU and mitomycin C. In the EORTC trial [12] 110 patients with advanced anal cancers (T3, 4 any N, and any T, N+) were treated. Radiotherapy consisted of 45 Gy with a daily dose of 1.8 Gy for five weeks. The treatment fields covered the small pelvis with the upper border at the promontorium, the distal border 3 cm below the tumor and the lateral borders 1.5 cm lateral to the pelvic rim. Patients without lymph node metastases were treated with a three- or four-field technique. In N+ patients, the treatment field included the inguinal area; two opposing AP-PA fields were used. After a rest period of six weeks, a clinical evaluation was carried out. Patients with stable disease or minor regression <50% went to surgery; those with at least a partial remission were treated with a radiation boost of 15 Gy for clinical complete remission or 20 Gy for clinically partial remission. The boost was given either with three to four field photon beam technique, by a single perineal electron beam field, or by brachytherapy. Chemotherapy consisted of 5-FU, 750 mg/m² continuous infusion from day 1 to day 5 and days 29-33 and mitomycin C, 15 mg/m² on day 1. No chemotherapy was given during the boost.

The addition of concomitant 5-FU-mitomycin C chemotherapy to full-dose radiotherapy resulted in an increase of local control. The complete remission rate increased from 54% to 80%, by adding chemotherapy to radiotherapy. After protocol treatment, which includes surgery in case of nonresponding or persistent tumor, the complete remission rate was 85% for radiotherapy alone and 96% for the combined approach. This difference in complete response remained visible during follow-up and resulted in a significantly lower local recurrence rate (p = 0.02) (Fig. 1) in the combined treatment group, showing an actuarial 18% difference at five years. Colostomy-free survival also improved in the combined treatment group, with an increase of 36% at five years (p = 0.002) (Fig. 2).

There was no significant difference in the nonhematological acute side effects between the two treatment arms. Chemotherapy had to be reduced in the second cycle for 19 patients, in 13 of them due to hematological toxicity. One fatality occurred due to septic shock during the third week of treatment. No significant increase in late side effects was observed, considering each late complication independently or on an actuarial basis as severe toxicity-free survival. The only exception was an increased amount of anal ulceration in the combined treatment group. There were four colostomies in each group due to late sphincter injury. There was no difference for overall survival or time to distant metastases (Fig. 3).

**Figure 1.** Locoregional control after protocol treatment including surgery for no response or residual disease: radiotherapy only (RT) or concomitant radiotherapy and chemotherapy (RT + CX). No change or residual tumor six weeks after completion of treatment was considered as failure at the time of randomization (p = 0.02, log rank test) (EORTC). Used with permission from [12].

**Figure 2.** Colostomy-free interval (p = 0.002 log rank test) (EORTC). RT = radiotherapy only; RT + CX = concomitant radiotherapy and chemotherapy. Used with permission from [12].

**Figure 3.** Overall survival for patients treated with radiotherapy only or concomitant radiotherapy and chemotherapy (p = 0.17 log rank test) (EORTC). RT = radiotherapy only; RT + CX = concomitant radiotherapy and chemotherapy. Used with permission from [12].
The UKCCCR trial [13] aimed at the same comparison as the EORTC study. A total of 585 patients of all tumor stages were randomized with about 50% advanced tumors (T3, T4) and around 20% with enlarged nodes. Radiotherapy was delivered by opposing fields, 45 Gy with daily doses of 1.8 or 2 Gy in four or five weeks, according to local practice. The boost was given after a rest period of six weeks via a perineal field or by brachytherapy. Chemotherapy consisted of 5-FU given continuously during the first and the fifth week, either 1,000 mg/m²/d, days 1-4 or 750 mg/m²/d, days 1-5, mitomycin C as a single dose of 12 mg/m² on day 1, reduced to 8 mg/m² in aged and sick patients. Treatment results revealed a drop in local failure rate at three years from 61% for the radiotherapy-alone arm to 39% for the combined group (Fig. 4). In this study, local failure was defined to be local recurrence as well as surgery due to severe local complication. There was no significant difference in overall survival, with 58% (radiotherapy) versus 65% (combined treatment) at three years (Fig. 5). Mortality from anal cancer, however, was significantly higher in the radiotherapy-alone group (39% versus 28%). Early toxicity was significantly increased in the combined treatment group, mostly attributable to hematological problems ($p = 0.03$); two toxic deaths occurred in the first phase of the trial. After reduction of mitomycin C for aged patients and antibiotic prophylaxis, no further problems occurred. There was no difference in late morbidity, with 10 colostomies in total attributed to damage of the anal sphincter in each group.

The Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group (RTOG/ECOG) Intergroup trial [14] defined the role of mitomycin C in the combined treatment of anal cancer. In a previous study, Cummings tried to omit the addition of mitomycin C due to severe toxicity in the combined treatment [11]. He found reduced efficacy of radiochemotherapy with 5-FU alone. In a phase III trial, 310 patients with all tumor stages (about 50% T3/T4, 17% N+), were randomized to receive 45 Gy given by AP/PA fields with a field reduction at 30 Gy. For N+ patients, the inguinal nodes were within the irradiation field. Chemotherapy consisted of 5-FU 1,000 mg/m²/d for 96 h, starting days 1 and 29. The mitomycin C group received 10 mg/m² of mitomycin C on days 1 and 29. One endpoint of the study was a negative biopsy six weeks after the end of primary treatment. In case of local failure, a salvage treatment was included in the trial with a boost of 9 Gy combined with an identical 5-FU administration and cisplatin 100 mg/m² for 6 h on day 2.

The results of that trial confirmed the importance of mitomycin C within the chemotherapy regimen. The rate of negative post-induction biopsies was different for both groups: 86% versus 92.6%, but this trend did not reach significance. The benefit was irrespective of tumor size. Tumor size itself was a significant prognostic factor for a negative biopsy ($p = 0.02$). There was a significant difference in colostomy rates (Table 2). At four years, there were 9% of mitomycin C and 5-FU-treated patients versus 23% of 5-FU-alone patients with colostomy ($p = 0.002$). The difference was more pronounced for T3/T4 tumors but did not reach significance for T1/T2 tumors (Figs. 6 and 7). The same significant difference emerges for colostomy-free survival at four years, with only very rare colostomies after the end of the second year.

There was a significant influence on disease-free survival, failure being defined as first disease progression, irrespective of the possibility of achieving local control by surgery. There were 73% of patients disease-free in the mitomycin C arm compared to 51% of the 5-FU-alone arm disease survival.

![Figure 4. Local failure rate: 15 patients died before assessment and were excluded from analysis. Number of events: radiotherapy 164, CMT 101 (RR = 0.54, CI 0.42-0.69, $p < 0.0001$). Under x-axis, number at risk = number event-free in each arm every year (UKCCCR). Used with permission from [13].](http://theoncologist.alphamedpress.org)

![Figure 5. Overall survival: Number of events: radiotherapy 125, CMT 111 (RR = 0.86, 95% CI 0.67-1.11, $p = 0.25$). Number at risk = number alive (UKCCCR). Used with permission from [13].](http://theoncologist.alphamedpress.org)
free at four years ($p = 0.0003$). For overall survival, there was no significant difference between the two groups, with a trend in favor of the mitomycin C group and fewer deaths from tumor reported.

Early toxicity was increased only for hematologic toxicity, with 7% versus 23% grade 4 and 0.7% versus 2.7% (one versus four patients) toxic deaths, all with neutropenic sepsis in the mitomycin C-containing regimen. Salvage treatment was carried out in 25 of 28 patients. In 12 of 22 post-salvage biopsies, no tumor was found. One-third of those patients remained disease-free, one-third were without disease after surgery, two died of tumor, and two of unrelated causes.

**Summary**

These three studies define a standard treatment in locally advanced anal cancer, which is radiotherapy with concomitant chemotherapy using continuous 5-FU in the first and fifth weeks and mitomycin C. There is a risk of neutropenic sepsis which is more pronounced with mitomycin C, but no difference in late tissue damage or late functional problems. This risk is outweighed by the benefit in terms of local control and colostomy-free survival, and also possible reduction of death from disease.

**OPEN QUESTIONS**

There are still some issues which must be clarified. The treatment option for small tumors, T1 and T2, N- is not clear. These patients were not included in the EORTC study, while the UKCCCR study did not stratify for stage; treatment results were not divided according to the different stages [13, 15]. In the Intergroup trial, the difference in negative biopsy rate after 45 Gy, local control, and colostomy rate was not significant for small tumors.

The problem of salvage treatment is dealt with only in the Intergroup trial. The dose of radiotherapy which is primarily used is 45 Gy, and this may be too low for advanced tumors. The doses of radiotherapy including salvage in the RTOG/ECOG trial were already similar to the European trials. Treatment time is an important factor in achieving local control in combined treatment. The long gap of six weeks may allow repopulation within the tumor. On the other hand, anal cancer has a known tendency to shrink only after a considerable period, and this has been the reason for this long gap.

The inclusion of mitomycin C in the treatment regimen has led to a better response in the RTOG trial but also leads to a significantly higher hematologic toxicity. Other squamous cell cancers show a good response if radiotherapy is combined

### Table 2. Frequency of patients with colostomy by treatment arm

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Colostomy*</th>
<th>n Colostomy*/total</th>
<th>% Colostomy**</th>
<th>n Colostomy**/total</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT + 5-FU</td>
<td>8.2</td>
<td>12/145</td>
<td>22</td>
<td>32/145</td>
</tr>
<tr>
<td>RT + 5-FU+MMC</td>
<td>3.4</td>
<td>5/146</td>
<td>9</td>
<td>13/146</td>
</tr>
</tbody>
</table>

Note: Colostomy designates colostomy, AP resection, and more extensive resection.

*Within 7 months of the start of treatment. **Actuarial estimate at four years. Used with permission from [14].

MMC = mitomycin C.
with 5-FU and cisplatin. It may be worthwhile to investigate in a phase III trial other drugs to replace mitomycin C [16-18].

It is obvious that surgery offers a chance for cure even after pretreatment with radiochemotherapy in selected patients. There is no agreement about the optimal time for surgical salvage. The slow shrinkage rate of anal cancers leads some investigators to wait for a second biopsy after four more weeks if the first post-treatment biopsy is positive before deciding to perform salvage surgery.

**ONGOING CLINICAL TRIALS**

Three ongoing studies deal with some of the open questions. The randomized RTOG/ECOG trial compares two radiotherapy schedules: 45 versus 59.4 Gy and two chemotherapy regimens, mitomycin C versus cisplatinum in combination with continuous 5-FU. The aim of this study is to achieve equal efficacy with less toxicity.

One French phase II trial starts with a neoadjuvant approach, giving two courses of cisplatin with continuous 5-FU radiochemotherapy. They also use cisplatin in the combined treatment.

**ONGOING CLINICAL TRIALS**

The current EORTC trial aims at increasing treatment effect for advanced tumors of >4 cm by reducing overall treatment time from 12 to 8.5 weeks and intensifying radiochemotherapy by adding continuous 5-FU at a low dose during the complete course of radiotherapy. Thirty-six Gy is given in four weeks to the whole pelvis. After a break of two weeks, all but progressing patients receive a boost of 23.4 Gy in two and one-half weeks. Mitomycin C is given at a dose of 10 mg/m² at the beginning of each radiotherapy period.

**CONCLUSION**

Multimodality treatment with radiotherapy and concomitant chemotherapy using mitomycin C and 5-FU leads to a high local control rate and preservation of the anal sphincter in the vast majority of patients.

**REFERENCES**


