Radiotherapy and Chemotherapy in the Conservative Treatment of Anal Canal Carcinoma

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Abstract. Aim: To evaluate the feasibility of conformal radiotherapy and concurrent chemotherapy in patients with anal canal carcinoma. Patients and Methods: Between 1990 and 2006, 83 patients affected by anal canal carcinoma were treated at the Radiotherapy Department of “La Sapienza” University of Rome. In all patients, a daily dose of 1.8 Gy, five times per week, was given for a total dose of 45 Gy for the whole pelvis (CTV1) and of 55-60 Gy for the tumor bed (CTV2). In 63 patients, chemotherapy consisted of two cycles of 5-fluorouracil (5-FU) and mitomycin C (MMC) or cisplatin delivery during the first and last week of radiotherapy. Results: The median follow-up time for all patients was 56.2 months. Treatment response was considered complete in 53 patients (63.8%) and partial in 30 patients (36.1%). Local tumor relapse was observed in 13 patients (15.6%). The probability of overall survival for all patients at 5 years was 75%; 39% in patients who underwent radiotherapy alone and 85% in patients who underwent radiochemotherapy (p=0.0013). Concerning acute toxicity, 9 patients developed grade 1 skin toxicity (10.8%), 35 grade 2 (42.1%), 26 grade 3 (31.3%) and 3 grade 4 (3.6%); eleven patients had grade 2 diarrhea (14.5%) and 2 grade 3 diarrhea (2.4%). Conclusion: This analysis suggests that the treatment scheme employed was effective for anal sphincter preservation and local control.

Cancer of the anal canal is a rare disease comprising only 1 to 5 percent of all carcinomas of the colon, rectum and anus (1-2). However, because of the greater spread of human papilloma virus and human immunodeficiency virus through sexual transmission, there has been a marked incidence of this disease over the last two decades. Until fairly recently, an abdominoperineal resection was the treatment of choice for tumors arising in the anal canal. This radical operation requires the removal of the anorectum, necessitating a permanent colostomy. This therapeutic approach has undergone dramatic changes since the publication by Nigro et al. (3). Primary therapy now consists of radiotherapy in combination with chemotherapy because this has yielded comparable survival rates to surgery, with the compelling advantage of sphincter preservation (4-5). This retrospective analysis intends to report results on patients with anal canal carcinoma treated with radiotherapy combined with chemotherapy based on 5-fluorouracil (5-FU) and mitomycin C (MMC).

Patients and Methods

Between 1990 and 2006, 83 patients affected by anal canal carcinoma were treated at the Radiotherapy Department of “La Sapienza” University of Rome. According to UICC-TNM (1997) staging classification (6), the clinical stage distribution of patients was as follows: T1/T2-N0 35 patients (42.1%), T3-N0 11 (13.2%), T4-N0 4 patients (4.8%), T2-N1 6 (7.2%), T3-N1 4 (4.8%), T2-N2 6 (7.2%), T3-N2 3 (3.6%), T2-N3 4 (4.8%), T3-N2 3 (3.6%), T3-N3 1 (1.2%), T4-N1 3 (3.6%) and T4-N3 3 patients (3.6%). Radiation therapy alone was used for 20 patients because they were not of a clinical condition to receive chemotherapy.

Each patient was immobilized and underwent planning CT scans in the prone position. Radiopaque markers were placed by the radiation oncologist on the skin surface of the patient at the presumed isocenter plane (midplane of the pelvis) to determine the zero plane for the CT images. In addition, radiopaque markers were placed at the anal verge for reference. With 0.5-cm slice thickness, the pelvis was scanned from the third lumbar vertebra down to 5 cm caudal from the anal marker. These CT images were imported into the treatment planning system and used to define the treatment fields.

All patients received whole-pelvic irradiation with the upper limit at the level of L5-S1 by means of four fields. The clinical target volume (CTV) was outlined and defined as: CTV1: anal canal, perirectal nodes, external and internal iliac nodes, obturator nodes and inguinal nodes; CTV2: entire initial tumor bed and positive lymph nodes. Organs at risk included the femoral head and neck, rectum, bladder and bowel.

Daily doses of 1.8-2 Gy, five times per week, were used for a total dose of 45 Gy for the whole pelvis (CTV1) and of 55-60 Gy for the tumor bed (CTV2). The photon energy used was given by a 6 or 15 Gy linear accelerator. In patients with groin disease, a boost to the inguinal lymph node was delivered with an energy of

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6, 9 or 12 MeV. Customised beam blocks or multileaf collimators were used to restrict the irradiation volume to the treated volume. The reference dose was specified at the intersection of the beam axis. The target absorbed dose was at least 90% and the maximum was not greater than 105% of the reference dose according to ICRU29 (7).

In 43 patients, chemotherapy consisted of two cycles of 5-FU and MMC delivery during the first and last week of radiotherapy. An 5-FU dose of 1000 mg/m²/24 h for 96 h was given by infusion. MMC was administered at a dose of 10 mg/m². In 20 patients chemotherapy consisted of two cycles of 5-FU and cisplatin (CDDP) delivery during the first and last week of radiotherapy. CDDP was administered at a dose of 50-75 mg/m².

The toxicity of treatment was evaluated and graded by means of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer criteria (8).

Patients were followed up with regular physical examinations, rectoscopy, blood counts, transanal-ecotomography and computed tomography. Follow-up was conducted every 3 months for the first 2 years, every 6 months in years 3 to 5, and once yearly subsequently. In case of no evidence of tumor, patients were evaluated by rectosigmoidoscopy and tumor bed biopsy. Estimates of survival rates and recurrence-free probabilities were calculated using the Kaplan-Meier product limit method.

Results

The median follow-up time for all patients was 56.2 months (range 4-168 months).

The treatment response, evaluated 90-180 days after the end of radiotherapy, was considered complete in 53 patients (63.8%) and partial in 30 patients (36.1%). Considering only patients who underwent combined radiochemotherapy (63 patients), the complete response rate was 69.8% (44 patients) and the partial response rate was 28.5% (18 patients). Seventeen patients (20.5%) were rescued by surgery, 12 (19.0%) treated by radiochemotherapy and 6 (30%) treated by radiotherapy alone. Local tumor relapse was observed in 13 patients (15.6%) from 12 to 48 months after the end of the treatment (median time 29.5 months). The probability of overall survival for all patients at 5 years was 75%: 39% in patients who underwent radiotherapy alone and 85% in patients who underwent radiochemotherapy (p=0.0013) (Figures 1 and 2).

The 5-year disease-free survival was 59% in patients who underwent combined treatment and 42% in patients treated with radiotherapy alone. The 5-year disease-free survival by clinical stage was as follows: I, 100%; II, 59%; IIIa 42%; and IIIb 30%. (Figure 3).

Concerning acute toxicity, all patients developed some type of skin reaction: based on RTOG criteria, 9 were grade 1 (10.8%), 35 grade 2 (42.1%), 26 grade 3 (31.3%) and 3 grade 4 (3.6%). Grade II leukopenia was observed in 11 patients (13.2%) and grade III in 3 patients (3.6%); eleven patients had grade 2 diarrhea (14.5%) and 2 had grade 3 diarrhea (2.4%). No patients had vomiting or dysuria. Regarding late toxicity, 3 patients developed grade 2 cutaneous toxicity and 1 patient had grade 2 chronic diarrhea approximately 12 months after the end of therapy. No patient was observed to have chronic leukopenia or significative alteration in sexual activity. Only one patient had penile necrosis due to vessel occlusion approximately 12 months after the end of treatment but it is not clear whether this event and radiochemotherapy were related.

Discussion

Combined modality therapy of radiation and concurrent chemotherapy, with intent to preserve anorectal function, has replaced surgery as the definitive treatment for epidermoid cancer of the anal canal (3, 9, 10). Although this strategy is considered standard for treatment, some questions still remain, including the optimal dose and volume of radiotherapy for adequate local control.

The Nigro protocol (3) used a low dose of 30 Gy in 15 fractions with concurrent chemotherapy but several studies (10-12, 26, 27) suggested a dose-response relationship for radiotherapy, especially for T3-T4 tumors. Constantinou et al. (11) reported a radiation dose response for local control of anal canal cancer treated with radiation given concurrently with chemotherapy. Local control improved with increasing radiotherapy doses from 50% for doses <54 Gy to 84% for doses >54 Gy. In 1996 the ROTG 92-08 (13) Phase II study was carried out using a radiation dose of 59.6 Gy combined with chemotherapy and in the same year the Eastern Cooperative Oncology Group study (14) reported a 68% complete response rate in 19 patients treated with 59.4 Gy combined with 5-FU and cisplatin. Recently, in a study of Ferrigno et al. (15) patients who received more than 50 Gy had a higher local control rate than those who received a dose ≤50 Gy (86.5% vs. 34%, p=0.012). The local control probability at 5 years was also higher among patients treated with more than 50 Gy but with a marginally significant difference: in this study patients who received >55 Gy and those who received a lower dose had a local control rate of 78.6% and of 79.3%. These data suggest that the optimal radiation dose is approximately 55 Gy. In our analysis the 5-year overall survival of 85%, the complete response of 63% and the 5-year disease-free survival of 59% are results similar to those reported in the literature (15-19) and these findings suggest that the treatment strategy used at our institution was effective for local control and sphincter preservation.

Another unanswered question is the optimal treatment volume of radiation for adequate locoregional control. Classically, anal canal lymphatic drainage involves the perirectal, obturator, inguinal and iliac nodes (20-21). On
the basis of these data, the CTV1 in our study included the anal canal and immediate perianal skin, and the perirectal, obturator and inguinal nodes; the CTV2 included the tumor bed and all macroscopic nodes seen at the initial evaluation. The inclusion of inguinal nodes, although recommended, still remains controversial.

The treatment strategy employed for inguinal node involvement is different: in many series radiochemistry is recommended (9, 15, 22) while in other institutions inguinal lymph node dissection followed by concurrent inguinal chemoradiation is the preferred treatment (21, 23, 24). In our experience, 10 patients presented inguinal node involvement at diagnosis and were treated with chemotherapy and radiotherapy to this region with a total dose of 59.4 Gy. In 8 of these patients, radiation to the groin area was administered utilizing 6 MeV photons for a dose of 45 Gy followed by an electron field boost of 14.4 Gy; in 2 patients dose to inguinal lymph nodes was administered utilizing 6 MeV photons for the total dose of 59.4 Gy. All patients obtained control of inguinal node disease after radiotherapy and no cases of femoral neck necrosis were encountered.

The management of a normal inguinal area also lacks a standard approach. In some institutions (15, 23-25) a wait-and-see policy with close follow-up is preferred, however in >15% of patients (especially those with T3-T4 tumors) an inguinal recurrence will occur (21, 28) and may lead to pelvic or metastatic evolution. In other series an elective irradiation of bilateral inguinal areas was performed (9, 18-20).

The optimal dose to control subclinical lymphatic disease has not yet been defined: in some Canadian and American institutions anal canal cancer is considered very radiosensitive and low doses of treatment to control subclinical disease (30-40 Gy) (20, 22) are favored. Conversely, European institutions (12, 17-19, 23) prefer a dose of 45-55 Gy. In our study, inguinal lymph node areas not involved in disease were included in CTV1 and received a dose of 45 Gy. All achieved inguinal control.

Systematic irradiation of the groin demands a larger volume of radiotherapy, which is related to an increase in

Figure 1. Survival probability for all patients.

Figure 2. Survival probability for combined radiotherapy and chemotherapy treatment (---) and for radiotherapy alone (---).

Figure 3. Disease-free survival by clinical stage.
toxicity, especially when associated with chemotherapy (21). In order to avoid side-effects, a new technique has been introduced: elective sentinel lymph node dissection using a standard technique with blue dye and radioactive technetium (29-31). The procedure is still in the early phase of investigation but appears to be a promising method to assess inguinal lymph node status and to guide individual therapeutic decisions.

Conclusion

Chemoradiotherapy is now widely accepted as the primary treatment modality for squamous cell cancer of the anus. While randomised trials have clearly shown combined therapy to be more effective than radiotherapy alone, there remains uncertainty over the optimal dose and volume of treatment. This retrospective analysis suggests that the treatment strategy used was effective in terms of local control, disease-free survival and sphincter preservation.

References


