Combined Chemoradiation Therapy for Anal Cancer

A Report of 56 Cases

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Fifty-six consecutive patients with primary epidermoid cancer of the anus were treated with combined chemoradiotherapy (CRT). No patient had been previously treated. There were 44 women and 12 men, with an age range of 25 to 88 years (median, 62 years). Cancer was located at the anal verge in five and at the anal canal in 51 patients. The tumor extended from the canal to adjacent sites in 37 cases. All patients had their tumors histologically assessed: 54 were squamous cell and two were basaloid carcinoma. Twelve patients had T1, 27 had T2, and 17 had T3 primaries, and eight had inguinal metastatic nodes. The protocol treatment consisted of three cycles of 5-fluorouracil (FU) (750 mg/m^2/day × 5 days continuous infusion) and mitomycin C (MMC) (15 mg/m^2 intravenous (I.V.) bolus on day 1 of each course) given every 6 weeks. Radiotherapy (RT) was started simultaneously: 36 Gy was given in 4 weeks to the anal region with perineum and the lower and middle pelvis, including inguinal and external iliac nodes. After 2 weeks of rest, a boost of 18 Gy was delivered to the anoperineal region in 10 fractions. Because of toxicity, the planned treatment was performed in 50% of patients: 28 patients received less than three cycles of chemotherapy, and seven patients received less than 49 Gy radiation therapy. Toxicities were mild to moderate, and no patients needed hospitalization. A complete response (CR) was observed in 49 patients (87%), eight of whom had metastatic nodes. A partial response (PR) was assessed in five patients (9%) and stable and progressive disease in 2 patients (4%). Objective response (OR) had no evident relationship with extent of primary, presence of metastatic nodes, number of cycles of chemotherapy, and doses of radiotherapy. Of 49 patients who achieved CR, 12 (24%) developed a local recurrence after a median interval of 8 months (range, 2 to 45 months); 11 of them were submitted to surgical rescue and 8 are alive without evidence of disease. Local recurrence was correlated with the main characteristics of patient and tumor and with treatment, but no clear correlation was observed. Actuarial survival rate at 5 years was 81%. Results of present study are compared with those reported by others, and crucial questions concerning combined chemoradiationtherapy are discussed. The authors conclude that chemoradiotherapy is a highly effective treatment of anal cancer, which should be employed as primary approach regardless of different characteristics of patient and tumor.

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OVER THE PAST 15 years, several investigators[1-20] have reported the consistent results of treating anal cancer by the combined chemoradiation therapy (CRT), according to the protocol initially reported by Nigro et al. in 1974.[1] Complete regression of the anal tumor was achieved in 59%[17] to 95%[7] of patients, and 5-year survival rate ranged from 70[12] to 100%.[18]

Anal cancer is, however, a relatively rare tumor, and institutional series are numerically poor and often accrued over several years. As shown in Table 1, no institute has treated more than a few dozen patients with CRT; moreover, treatment protocols vary regarding radiation or chemotherapy schedules. The wide ranges in criteria of selection, staging, and evaluation of results make comparisons between different series even more difficult (Table 1). In spite of these limitations, which do not allow selection of the best treatment in confirmed cancer patient groups, CRT is quoted as the preferred treatment for anal cancer and surgery, namely abdominoperineal resection (APR), is reserved for patients with residual tumor or local recurrence.[14]

On this basis, in 1981 we started to treat patients bearing previously untreated anal cancer with an aggressive protocol that provided three cycles of 5-fluorouracil (FU) plus mitomycin C (MMC) and concomitant irradiation consisting of 36 Gy in 20 fractions to primary tumor and pelvis, including inguinal nodes and a boost of 18 to 20 Gy to the anoperineal region, plus or minus inguinal sites.

The authors report their experience on 56 patients treated with CRT for epidermoid cancer of the anus.

Materials and Methods

From August 1981 to December 1989, 56 consecutive patients with primary epidermoid cancer of the anus were

TABLE 1. *Combined Chemoradiation Treatment in Anal Cancer: Survey of Institutional Series*

Author	Institution*	No. of Patients	RT Dose (Gy)	Chemotherapy†	CR (%)	Local Recurrence (%)	Survival Rate (5 yr)
Sischy et al.[7]	HHR	19	40–64	A	95	0	NS
Nigro[13]	CS	104	30	A	90	12	NS
Cummings et al.[12]	PMH	30	50	D	93	0	70
Meeker et al.[16]	CS	19	30	A	88	14	86 (3 yr)
Enker et al.[17]	MSKCC	44	30	C	59	23	70
Flam et al.[18]	UCSF	30	41–50	B	87	4	100
Habr-Gama et al.[19]	HCU	30	30–45	A	73	4	NS
Nigro et al.[20]	WSU	44	30	A	88	11	79

* HHR, Highland Hospital, Rochester, New York; CS, collected series; PMH, Princess Margaret Hospital, Toronto, Ontario, Canada; MSKCC, Memorial Sloan-Kettering Cancer Center, New York, New York; UCSF, University of California, San Francisco, California; HCU, Hospital das Clinicas of the University, Sao Paulo, Brazil; WSU, Wayne State University, Detroit, Michigan.

† A, FU 1000 mg/m^2/day × 4 q28 day × 2 MMC 15 mg/m^2 day 1; B, FU 1000 mg/m^2/day × 4 + MMC 15 mg/m^2 day 1 × 2 q28 day; C, FU 750 mg/m^2/day × 5 + MMC 10–15 mg/m^2 day 1; D, FU 1000 mg/m^2/day × 4 + MMC 10 mg/m^2 day 1; NS, not stated.

treated with a combination of chemoradiation at the Istituto Nazionale Tumori of Milano. No patient had been previously treated for anal cancer. This was histologically assessed in all patients before referral for combined modality treatment.

There were 44 women and 12 men; at presentation, age ranged from 25 to 88 years (median, 62 years). Five patients had the cancer located at the anal verge and 14 at the anal canal; in 37 patients, the tumor extended from the canal to adjacent sites (rectum, anal verge, rectovaginal septum).

The histology of primary tumors included two basaloid and 54 squamous cell carcinomas, which resulted, according to histopathologic grading, in eight well-differentiated (G1), 24 moderately differentiated (G2), and 12 poorly differentiated (G3); in 10 tumors the grading was not otherwise specified (NOS).

The series was correctly reclassified according to the most recent TNM (tumor, nodes, metastases) classification (1987),[21] because the main feature of the tumor—site, size, infiltration, regional lymph node status—were accurately recorded. The distribution of cases according to TNM criteria is reported in Table 2: eight patients (14%) had metastases at inguinal lymph nodes; perirectal or mesenteric metastases were not detected.

Before treatment, all patients underwent endoscopic examination of the anus and rectum, chest x-ray, complete blood evaluation, and ultrasound examination of the upper abdomen and pelvis. Lympho-angiography was performed in a routine way in the first 26 patients; only three patients had positive lymphangiograms: one was a false positive; in one case, clinically evident metastatic nodes were confirmed; in the third one, subclinical positive nodes were diagnosed. For this outcome, the diagnostic procedure was not considered particularly useful, and thus it was abandoned. Enlarged nodes were always investigated with fine needle aspiration or surgical biopsy.

The treatment protocol consisted of three cycles of 5-fluorouracil (FU) and mitomycin C (MMC) concomitant with pelvic irradation. Mitomycin C 15 mg/m^2 was given as a bolus intravenous injection on day 1; a 24-hour infusion of FU 750 mg/m^2 was begun on day 1 and continued for 5 consecutive days. The cycle was repeated after 6 weeks, depending on the level of hematologic toxicity.

Radiotherapy was started on the same day. The target of irradiation was the anal region with perineum and lower and middle pelvis, including inguinal and external iliac nodes. Two anteroposterior and posteroanterior opposed fields were used, and a daily dose of 1.8 Gy (0.9 + 0.9) was given through both portals, up to a total dose of 36 Gy at midplane in 4 weeks, with a 6 MeV linear accelerator. After 2 weeks' rest, at 6 weeks from the beginning of treatment, a second cycle of chemotherapy was scheduled and radiotherapy was simultaneously started again. A direct field was tailored to the anoperineal region, and 10 fractions of 1.8 Gy were given in 2 weeks. The dose was calculated according to the site and depth of the tumor to give the full dose to the proximal margin of the original lesion. In case of positive inguinal nodes, they were boosted with electrons. The scheduled total dose to the

TABLE 2. *Staging of 56 Anal Cancers According to TNM Classification (1987)*

Tumor (Maximum Diameter)	No. of Patients (%)	Regional Nodes (No. of Patients)	
		N−	N+
T1 (2 cm)	12 (21%)	11	1
T2 (2.1–5 cm)	27 (48%)	23	4
T3 (5 cm)	17 (30%)	14	3
Total	56	48	8

N−, no regional lymph node metastases; N+, metastases to regional lymph nodes.

tumor was 54 Gy. In a few cases with locally advanced disease, the dose of the boost was raised to 20 to 24 Gy. No case received more than 60 Gy. Patients were evaluated before every cycle. Two months after the end of the treatment, anoscopy with biopsy was performed; physical examination and complete blood test were repeated every 2 months during the first year, then every 4 months. Chest x-ray and ultrasound examination of the abdomen and pelvis were performed every 6 months.

All patients were evaluable for toxicity, which was graded according to the WHO criteria[22]; no patient was lost to follow-up. Criteria for evaluation of response were as follows: a complete response (CR) was defined by the clinical and histologic disappearance of tumor; a partial response (PR) was defined by a reduction of more than 50% in the product of the two largest diameters of the tumor. Stable disease (SD) was defined by unchanged tumor size. Progressive disease (PD) was defined by an increase over 25% in the product of the two largest diameters of the tumor or the appearance of new lesions.

Survival was calculated from beginning of treatment. Actuarial survival was calculated by the method of Kaplan and Meier.[23]

Patients dead of undetermined causes were considered dead of tumor and those dead without evident disease were considered as alive in the actuarial survival calculation.

Results

Feasibility of Combined Modality Treatment

The planned treatment was performed in 50% of patients: the three-cycle regimen of chemotherapy was delivered to 28 patients (50%), whereas the total radiation dose was inferior to the planned one in seven patients (12.5%). Table 3 summarizes the causes of reduction of doses and cycles. Twenty-five patients had less than three cycles of chemotherapy because of toxicity (19 patients), or because of age exceeding 75 years and poor general condition (six patients); however, these patients had achieved complete clinical and pathologic response. Three additional patients interrupted the treatment for different reasons: one died after the second cycle of acute pulmonary edema, one refused the treatment after one cycle of chemotherapy, in absence of relevant toxicity, and the third patient developed inguinal metastases after two cycles of chemotherapy.

TABLE 3. *Feasibility of Combined Modality Treatment in 56 Patients With Anal Cancer*

Treatment	No. of Patients (%)	Causes of Reduction	No. of Patients
Chemotherapy (cycles)			
3	28 (50%)	—	—
2	19 (34%)	Toxicity	15
		Age	2
		Progression	1
		Early death	1
1	9 (16%)	Toxicity	4
		Age	4
		Refusal of treatment	1
Radiation therapy (total doses Gy)			
49–60	49 (87%)	—	—
39–45	6 (11%)	Toxicity	5
		Early death	1
26	1 (2%)	Refusal of treatment	1

TABLE 4. *Acute Toxicity in 56 Patients Treated for Anal Cancer*

	Grade of Effect* †				
Toxic Effect	0	1	2	3	4
Hematologic	25	12	15	4	—
Stomatitis	30	24	2	—	—
Diarrhea	—	1	53	2	—
Proctitis	—	4	50	2	—
Dermatitis	—	2	51	3	—
Cystitis	26	30	—	—	—

* WHO classification.[23]
† No. of patients.

Radiotherapy was interrupted after 39 to 45 Gy because of acute local toxicity (five patients) and early death (one patient), whereas one patient refused the treatment after 26 Gy.

Toxicity

Acute toxic effects are reported in Table 4. All patients experienced diarrhea, proctitis, and perineal dermatitis starting after the second week of treatment. These symptoms were low grade in most of them and easily controlled with symptomatic treatments; in five patients, however, intestinal and local toxicity suggested interrupting the treatment. All patients recovered completely 2 to 8 weeks after completion of treatment. Mild transient stomatitis and cystitis were observed in 46% and 54% of patients, respectively. Hematologic toxicity was observed in 31 patients, 61% of whom had grades 2 and 3; toxicity forced reducing the number of cycles in 19 and lowering the doses of drugs in 13. No bleeding or neutropenic febrile episodes were observed. Two patients had cutaneous necrosis in the site of injection due to extravasation of MMC into subcutaneous tissue; both underwent surgical repair.

Late complications were recorded in two patients who had radio necrosis: one patient received an intracavitary radium implant because of partial response to primary treatment, and 6 months later developed an anal radiation ulcer that required a proximal colostomy; the other one had been irradiated 50 years before for a Hodgkin's lym-

phoma at unknown doses and sites; she developed a large radio necrosis of the presacral tissues 18 months after treatment.

Objective Response

Complete Response. The complete response of the anal cancer was clinically and histologically assessed in 49 patients (87%); eight of them who had metastatic nodes as well as inguinal metastases achieved CR. The reduction of the tumor was evident 1 month after the beginning of treatment, and it was generally complete within 2 months in all these patients.

Partial Response. A partial response was assessed in five patients: two of them interrupted the treatment because of early death and refusal of treatment; the other three patients had local radiation toxicity, and they received 40 to 55 Gy.

Stable Disease. One patient did not show relevant modifications of anal cancer after three cycles of chemotherapy and 56 Gy of radiotherapy; thus, he was submitted to APR; at laparotomy, hepatic metastases were detected. Because their presence before the combined treatment could not be excluded, the response to treatment was considered SD.

Progressive Disease. One patient developed lymph node metastases before the third cycle of chemotherapy; she was submitted to APR plus inguino-iliac monolateral dissection. The histologic examination confirmed persistent anal cancer and one metastatic inguinal node.

Table 5 summarizes the objective response according to the primary extent of the tumor: no evident relationship was found between T extent and objective response. This was correlated also with the number of cycles of chemotherapy delivered (Table 6). It is evident that the objective response rate — in other words, complete regression — was independent of the number of cycles.

Late Results

The median follow-up of this series was 49 months (range, 12 to 112 months). Forty-three patients (77%) are alive without evidence of disease after a median interval of 40 months from treatment (range, 12 to 112 months); seven patients (12.5%) died of cancer progression and four of unrelated disease. Two patients are still alive with disease, (one with local recurrence and one with hepatic metastases) 14 and 37 months after the treatment.

TABLE 5. *Objective Response by Tumor Extent After Combined Modality Treatment in 56 Patients*

Tumor Extent	Response			
	CR	PR	SD	PD
T1 (12 patients)	9	2*	1	—
T2 (27 patients)	27	—	—	—
T3 (17 patients)	13	3†	—	1
Total (56 patients)	49 (87%)	5 (9%)	1 (2%)	1 (2%)

* One early death.
† One refusal of treatment.
CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

TABLE 6. *Objective Response According to Number of Cycles of Chemotherapy*

No. of Cycles	No. of Patients With Objective Response			
	CR	PR	SD	PD
3 (28 patients)	24 (86%)	3	1	—
2 (19 patients)	17 (89%)	1	—	1
1 (9 patients)	8 (88%)	1	—	—

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

The results according to objective response were as follows:

Complete Response. Out of 49 patients who achieved complete response, 12 (24%) developed a local recurrence (Table 7); 11 of them underwent surgery and one additional CRT (one cycle of chemotherapy synchronous with 30 Gy through a direct limited field) because the recurrence as well as the primary tumor was not resectable. Eight of these recurred patients are alive without evidence of disease; three died of tumor progression and one is alive with disease (local recurrence). Three patients developed distant metastases (lung, liver, para-aortic nodes) without local recurrence and died of progressive disease; two patients died of unrelated disease. Therefore, 32 patients (57%) can be considered as cured by CRT alone to date. Local recurrence was correlated with the main characteristics of patient and tumor, in other words, sex, age, site and stage of primary, histology, doses of radiochemotherapy, but no clear correlations were observed.

Partial Response. Three patients submitted to surgery are alive without evidence of disease, and one is alive with hepatic metastases.

TABLE 7. *Local Recurrence Rate in 49 Patients With Complete Response After Combined Treatment and Type of Treatment of the Recurrence*

Tumor Extent	No. of Local Recurrences (%)	Disease-Free Period (mo) (range)	Treatment
T1 (9 patients)	1 (11%)	45	1 LE
T2 (26 patients)	7 (27%)	12 (3–18)	6 APR 1 CTR + LE
T3 (14 patients)	4 (29%)	4 (2–10)	3 APR 1 CRT
Total (49 patients)	12 (24%)	8 (2–45)	

LE, local excision; APR, abdominoperineal resection; CRT, chemoradiation therapy.

Stable and Progressive Disease. Both patients died, one of hepatic metastases and the other of cardiac failure.

The actuarial 8-year overall survival was 81% (Fig. 1).

Table 8 reports the actual survival status. The median survival of patients that died because of the disease and of those who died of other causes was similar, but we can exclude that the latter had cancer recurrence.

TABLE 8. *Survival Status and Median Survival Period*

Status	No. of Patients (%)	Median Survival (mo) (range)
No evidence of disease	43	40 (13–101)
Alive with disease	2	25.5 (14–37)
Dead of disease	7	22 (15–36)
Dead of other causes	4	22.5 (2–28)

Discussion

Anal cancer is a rare tumor because it occurs in about 1% to 4% of all malignant tumors of the distal alimentary tract[24]; the value of a new treatment, for example, primary chemoradiation therapy, is therefore difficult to assess because a randomized prospective trial is not feasible in a single center; it also is difficult to plan as a multicentric study. In fact, if all institutional series are considered (Table 1), they cumulatively account for less than 300 patients treated with CRT over more than 15 years. It was evident, however, from the first reports [1,2,4,25] that this new therapeutic approach could upset the conventional treatment of anal cancer consisting of surgery or radiotherapy alone.

When we started with CRT in the early 1980s, we supposed that more aggressive treatment than those already reported could achieve a higher final control of the disease. In detail, three cycles of chemotherapy could both improve the therapeutic effects of radiation and give a better control of distant occult metastases. However, the radiation dose of 36 Gy, to a large volume, followed by an additional anoperineal boost of 18 to 20 Gy, could increase the locoregional control of the tumor, compared with the results achieved by authors giving lower total doses.

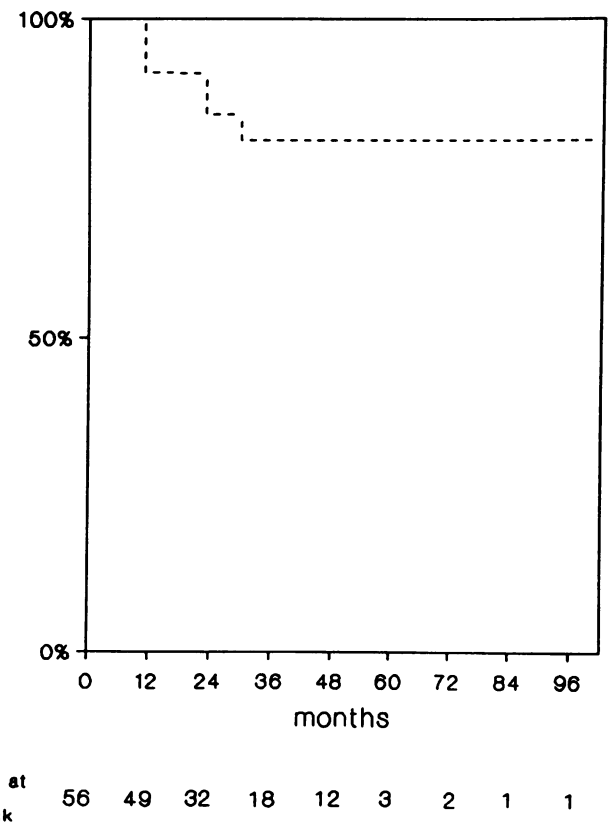

FIG. 1. Actuarial overall survival of 56 patients with anal cancer treated by combined chemoradiation therapy.

Our policy was later supported by reports of Sischy et al.[7] in 1982, Flam et al.[9] in 1983, and Cummings et al.[12] in 1984.

Our preliminary results were highly encouraging.[26] The long-term results in our first consecutive 56 patients, however, are not as good as initially expected, even if not worse than those generally reported in literature. Eighty-seven per cent of patients achieved complete response, 77% are disease free after a median follow-up of 40 months, and 5-year actuarial survival rate is 81%. Despite these excellent overall results, the local recurrence rate of 24% in our series is higher than figures reported in the three series[12,18,19] concerning patients treated with CRT alone. The reason for this unfavorable comparison is difficult to ascertain. In our series, the characteristics of patient and tumor did not appear significantly correlated with response to treatment and prognosis. In particular, the size of primary tumor did not influence either the objective response or the local recurrence and survival rates. Two patients with tumor of less than 2 cm in size failed to respond (one PR and one SD); one of them developed hepatic metastases too; both were keratinizing tumors of the anal canal without evidence of nodal metastases. Conversely, all 27 patients with tumors between 2 and 5 cm achieved complete response. Greenall et al.[15] also reported that the size of primary tumor did not appear to influence the presence or absence of tumors in the excised specimen, whereas others[17,18,20] considered the size of the tumor as one of the most important prognostic factors after CRT. Boman et al.,[27] after a pathologic survey of patients treated by surgery, reported that survival was strongly influenced by depth of tumor invasion, status of regional nodes, and histologic grade. Frost et al.[28] concluded that among clinical factors, sex, size, nodal status, and presence of distant metastases determined the prognosis.

Another point of discussion is the prognostic value of nodal metastases in patients treated by CRT. Although those operated on with metastases had poor prognosis[15,24,27,28] in our series, the eight patients with nodal metastases completely recovered and none showed either local or distant relapse. The patient who developed nodal metastases during treatment underwent lymphadenectomy and died 20 months after the treatment without evidence of cancer.

In three series,[7,12,18] there were cumulatively 19 patients with inguinal metastases at presentation. They achieved complete remission and were disease free at last follow-up. Of seven patients with inguinal metastastic nodes cumulatively reported by others,[17,19,20] five developed further metastases or local recurrence and died of disease. Therefore, the negative prognostic impact of nodal metastases could be modified by CRT, because 29 of 34 patients with proven inguinal metastases (85%) did not show recurrence.

Treatment is another factor that should be considered. In our experience, complete response and local recurrence rates were not influenced by the number of cycles of chemotherapy, but because of toxicity, the scheduled three cycles of chemotherapy could not be given to 50% of patients. Twenty-eight patients received three cycles, 19 received two cycles, and 9 received one cycle only, but no significant differences of short-term and long-term results could be observed between the three groups. Data from literature on this topic are scanty and, if the results obtained with one[12,17] or two [7,13,16,18–20] cycles are compared, no relevant differences are evident (Table 1).

The optimal regimen of radiotherapy, as well as for chemotherapy, has not yet been defined. The complete response rate of patients who received 30 Gy of irradiation was 80% *versus* 79% of patients receiving higher doses usually given through a split-course regimen. The split-course technique had to be adopted to avoid short-term and long-term side effects. One patient in our series required colostomy because of anal necrosis due to complementary interstitial implant. All patients retained normal sphincteric and enteric functions. It is impossible to verify if the split-course technique played an unfavorable part in terms of recurrence rate after CR, allowing repair and repopulation of cancer cells during the interval between the two courses of radiotherapy.

It is evident that further studies are needed for a better understanding of factors affecting the results of CRT. These factors could differ from those stated by studies on natural history or results of surgery.

To our knowledge, one randomized clinical trial only has been activated by the European Organization for Research and Treatment of Cancer cooperative groups of the Radiotherapy and Gastrointestinal Group in 1987. In this trial, chemoradiotherapy *versus* radiotherapy alone are compared; no preliminary information on results are yet available.

The most surprising result from our experience and from the literature is the similar favorable efficacy of very different therapeutic schedules providing from a minimum of one cycle of chemotherapy and 30 Gy of radiotherapy up to three cycles of chemotherapy and total radiation doses of 64 Gy. It could be hypothesized that the most effective and relevant factor for the efficacy of the combined treatment is the synchronous effect of radiotherapy and chemotherapy, given at the same time and not in sequence. A more than additive or synergistic effect of the two treatments could be the main reason of success.

Apart from the difficult explanation of some events, however, clear evidence does exist that combined chemoradiotherapy is a highly effective treatment of anal cancer, which should be employed as primary approach regardless of different characteristics of patients and tumor. It is possible that a drug combination different from standard FU-MMC could achieve better results. Flam et al.[18] reported effective salvage treatment employing different associations of FU, MMC, cisplatin, and methotrexate in combination with additional radiation therapy. In the Houston report of Hughes and colleagues,[29] continuous infusion of FU during the whole course of radiotherapy yielded excellent results without toxicity.

Surgery should be carried out when residual tumor or local recurrences are detected. In our series, 12 of 19 patients failing primary treatment were cured by surgical rescue.

A careful follow-up is recommended for at least 5 years because local recurrences were detected up to 45 months after primary therapy.

References

1. Nigro ND, Vaitkevicius VK, Considine B Jr. Combined therapy for cancer of the anal canal. Dis Colon Rectum 1974; 17:354–356.
2. Newman HK, Quan SHQ. Multi-modality therapy for epidermoid carcinoma of the anus. Cancer 1976; 37:12–19.
3. Quan SHQ, Magill GB, Leaming RH, Hajdu SI. Multidisciplinary preoperative approach to the management of epidermoid carcinoma of the anus and anorectum. Dis Colon Rectum 1978; 39: 89–91.
4. Bruckner HW, Spigelman MK, Mandel E, et al. Carcinoma of the anus treated with a combination of radiotherapy and chemotherapy. Cancer Treat 1979; 63:3951–3958.
5. Nigro ND, Vaitkevicius VK, Buroker T, et al. Combined therapy for cancer of the anal canal. Dis Colon Rectum 1981; 24:73–75.
6. Wanebo HJ, Futrell W, Constable W. Multimodality approach to surgical management of locally advanced epidermoid carcinoma of the anorectum. Cancer 1981; 17:2817–2826.
7. Sischy B, Remington JH, Hinson EJ, et al. Definitive treatment of anal-canal carcinoma by means of radiation therapy and chemotherapy. Dis Colon Rectum 1982; 25:685–688.
8. Smith DE, Muff NS, Shetabi H. Preoperative radiation and chemotherapy for anal and rectal cancer. Am J Surg 1982; 143:595–598.
9. Flam MS, John M, Lovalvo LJ, et al. Definitive nonsurgical therapy of epithelial malignancies of the anal canal: a report of 12 cases. Cancer 1983; 51:1378–1387.
10. Michaelson RA, Magill GB, Quan SHQ, et al. Preoperative chemotherapy and radiation therapy in the management of anal epidermoid carcinoma. Cancer 1983; 51:390–395.

11. Nigro ND, Seydel HG, Considine B, et al. Combined preoperative radiation and chemotherapy for squamous cell carcinoma of the anal canal. Cancer 1983; 51:1826–1829.
12. Cummings B, Keane T, Thomas G, et al. Results and toxicity of the treatment of anal canal carcinoma by radiation therapy or radiation therapy and chemotherapy. Cancer 1984; 54:2062–2068.
13. Nigro ND. An evaluation of combined therapy for squamous cell cancer of the anal canal. Dis Colon Rectum 1984; 27:763–766.
14. Leichman L, Nigro N, Vaitkevicius VK, et al. Cancer of the anal canal: model for preoperative adjuvant combined modality therapy. Am J Med 1985; 78:211–215.
15. Greenall MJ, Quan SHQ, Urmacher C, DeCosse JJ. Treatment of epidermoid carcinoma of the anal canal. Surg Gynecol Obstet 1985; 161:509–517.
16. Meeker WR, Sickle-Santanello BJ, Philpott G, et al. Combined chemotherapy, radiation and surgery for epithelial cancer of the anal canal. Cancer 1986; 57:525–529.
17. Enker WE, Heilwell M, Janov AJ, et al. Improved survival in epidermoid carcinoma of the anus in association with preoperative multidisciplinary therapy. Arch Surg 1986; 121:1386–1390.
18. Flam MS, John MJ, Mowry PA, et al. Definitive combined modality therapy of carcinoma of the anus: a report of 30 cases including results of salvage therapy in patients with residual disease. Dis Colon Rectum 1987; 30:495–502.
19. Habr-Gama A, Da Silva AH, Nadalin W, et al. Epidermoid carcinoma of the anal canal: results of treatment by combined chemotherapy and radiation therapy. Dis Colon Rectum 1989; 32: 773–777.
20. Nigro ND, Vaitkevicius VK, Considine B Jr. Dynamic management of squamous cell cancer of the anal canal. Invest New Drugs 1989; 7:83–89.
21. International Union Against Cancer (UICC) TNM Classification of Malignant Tumours. New York: Springer-Verlag, 1987, ISBN 3-540-17366-8.
22. WHO/UICC. Handbook for Reporting Results of Cancer Treatment. WHO Offset Publication No 48, Geneve, 1979.
23. Kaplan EL, Meier P. A non-parametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457–481.
24. Mitchell EP. Carcinoma of the anal region. Semin Oncol 1988; 15: 146–153.
25. Buroker T, Nigro ND, Considine B Jr, Vaitkevicius VK. Mitomycin C, 5-fluorouracil and radiation therapy in squamous cell carcinoma of the anal canal. *In* Corte S, Crooke S, eds. Mitomycin C. New York: Academic Press Inc, 1979, pp 183–188.
26. Zucali R, Doci R, Bombelli L. Combined chemotherapy-radiotherapy of anal cancer. Int J Radiat Oncol Biol Phys 1990; 19:1221–1223.
27. Boman BM, Moertel CG, O'Connel MJ, et al. Carcinoma of the anal canal: a clinical and pathological study of 188 cases. Cancer 1984; 54:114–125.
28. Frost DB, Richards PC, Montague ED, et al. Epidermoid cancer of the anorectum. Cancer 1984; 53:1285–1293.
29. Hughes L, Rich TA, Delclos L, et al. Radiotherapy for anal cancer: experience at M.D. Anderson Hospital 1979–1987 (abstr). Int J Radiat Oncol Biol Phys 1989; 15(Suppl):115–116.