Conservative treatment for carcinoma of the anus – a report of 35 patients

K. Serkies, E. Bednaruk-Mlynski, R. Dziadziuszko, J. Jassem

Department of Oncology and Radiotherapy, Medical University of Gdansk, 80-211 Gdansk, Poland, e-mail: onkol@amedec.amg.gda.pl

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Conservative treatment for carcinoma of the anus has become the standard care for this malignancy. In this study we report on our experience with this method with particular emphasis on treatment outcome and acute toxicity. Between April 1991 and February 2002, 35 patients (male/female ratio 0.35) with UICC $T_{1-i}N_{0-3}M_0$ squamous cell carcinoma of the anal canal or anal margin were treated with chemo-radiation (31 patients) or radiotherapy alone (4 patients). Three patients had previously undergone local tumor excision with anus preservation. The total tumor dose of 48 to 60 Gy was delivered either by split-course or continuous radiation therapy to the pelvis, followed by a local boost to the primary tumor. Chemotherapy included one or two cycles of mitomycin C (10–15 mg/m^2 day 1) and 5-fluorouracil (450–750 mg/m^2 day 1 to 4 or 5) given during the first and the last part of irradiation. Complete tumor remission was obtained in 26 (76%) out of 34 evaluable patients. Clinically persistent disease was found in five (17%) and three (7%) patients treated with chemo-radiation and radiation alone, respectively. In four of these cases salvage surgery was performed. With a median follow-up of 49 months (range 2–131 months) local recurrence occurred in four patients (12%), and distant metastases – in two (6%). Overall, local treatment failure was observed in twelve patients (35%) including eight with T_3 and one with T_4 tumor. Local control was maintained until the last follow-up or death in 22 patients (65%). An actuarial 5-year overall and colostomy-free survival rates were 63% (CI, 45–81%) and 45% (CI, 25–64%), respectively. Nineteen patients (54%) experienced acute toxicity, predominantly hematologic and gastrointestinal, and severe effects including one death occurred in 11 patients (31%). Late sequelae including chronic diarrhea, edema of genitalia and legs, impaired sexual activity, and bone fractures were observed in eight patients (24%). Moderate anal stool incontinence occurred in three patients (9%). In conclusion, conservative management of anal carcinoma allows durable colostomy-free survival in a proportion of patients. However, the risk of local failure is relatively high in patients with large primary tumors. Combined chemo-radiation is associated with relatively high rate of acute toxicity.

Key words: Anal carcinoma, radiation, chemo-radiation, normal tissue reactions.

Cancer of the anus is a rare malignancy, representing approximately 5% of the lower gastrointestinal tract tumors. This neoplasm is divided into two groups: cancer of the anal canal and cancer of the anal margin. Anal cancers are more common in women and the median age at diagnosis is about 60 years [2]. The risk of this tumors increases in human immunodeficiency virus (HIV)-infected patients. Malignancies arising from the epithelium of the anus are mostly squamous cell of various types including cloacogenic, basaloid, transitional, or mucoepidermoid carcinomas. Most of these tumors are poorly or moderately differentiated. They grow in a diffuse manner and infiltrate widely beyond palpable mass. Recently, sphincter sparing therapy has widely replaced previously used abdominoperineal resection as the standard first line treatment of anal cancer [1, 4, 5, 8, 14, 18, 24, 25]. Most commonly, conservative therapy consists of radiation therapy and concomitant chemo- radiotherapy with 5-fluorouracil (5-FU) and mitomycin C (MMC), as introduced by Nigro et al in 1974 [17]. Surgery is now reserved for recurrent tumors and tumors resistant to conservative therapy.

Conservative therapy of anal cancer was introduced at our institution in 1991. In the present article we present our experience with this method.

Material and methods

This retrospective review includes a series of 35 consecutive patients (26 females and 9 males) with localized histo-

logically proven squamous cell carcinoma of the anal canal (32 patients) or anal margin (three patients) treated with chemo-radiation or radiation therapy alone between April 1991 and February 2002 (Tab. 1). Before the irradiation three patients had undergone incomplete local excision, defined as microscopic involvement of surgical margins in two patients and macroscopic residual disease in one. Apart from full medical history, pre-treatment evaluation in all patients included physical and digital rectal examination and additionally gynecological examination in women, proctoscopy, routine labolatory tests, chest X-ray, abdominal and pelvic ultrasound or computed tomography. The latter was usually performed with barium enema. Enlargement of inguinal nodes was seen in 11 patients, of whom in ten nodal involvement was microscopically confirmed by fine needle aspiration biopsy. Associated local conditions included chronic fistula in one patient, and hemorrhoids in two. Three patients had been previously treated with immunosuppressive agents due to chronic lymphocytic leukemia (two patients) and lupus (one patient). Additionally, one patient had a history of prolonged treatment with prednisolone for chronic hepatitis.

Follow-up ranged from 2 to 131 months (median, 49 months) from the beginning of the treatment. Complete data was obtained for all patients.

Treatment methods. Thirty one patients were treated with chemo-radiation and four with external beam radiation therapy (EBRT) alone (Tab. 2). In the former group 29 patients received the split-course irradiation consisting of the initial dose to the pelvis (the planned dose was 30 Gy) followed by the boost to the tumor, and the remaining two patients received conventional pelvic EBRT at a total tumor dose of 50 and 60 Gy. In all but one patients pelvic irradiation was performed with two parallel- opposed fields, the remaining case was irradiated with 4-field (box) technique. Patients were treated with linear accelerator or ^{60}Co machine. The supine position was mostly used to treat the pelvis and groin. The upper border of the AP-PA fields extended to the superior border at L5–S1 (in some patients to the L4–L5 interspace) or to the bottom of the sacroiliac joints. The lateral borders of the fields extended to 1–1.5 cm lateral to the bony pelvis or lateral to include the involved/clinically suspected inguinal nodes. The treatment portals in all cases included the anal sphincter and the entire perineum. The blocks shielding lower corners of the fields and a part of inquinal region were routinely used. In split-course group, after a planned gap of 7 days (actual gap 3–31 days; median, 11.5 days) the second course of 10 to 30 Gy (median, 20 Gy) irradiation comprising tumor bed was per-

Table 1. Patient characteristics (n=35)

Variable	n
Age (years)	
Range	38–78
Median	60
Sex	
Female	26
Male	9
UICC stage	
$T_{1,2}$ N_0	13
$T_{3,4}$ any N	17
N_3, any T	5
Tumor localization	
Anal canal	32
Anal margin	3
Cell differentiation	
G1	4
G2	9
G3	6
Not determined	16

Table 2. Treatment characteristics

Variable	n
Treatment method	
Radiation alone	4
Chemo-radiation	31
Continuous	2
Split-course	29
Tumor dose – first part (Gy)	
Range	20–45
Median	30
Treatment rest period (days)	
Range	3–31
Median	11.5
Boost to the tumor (n=29)	
Tumor dose range (Gy)	10–30
Total tumor dose (Gy)	
Range	48–60
Median	50
Technique of EBRT	
AP-PA	34
4-field	1
Technique of the boost	
EBRT	
2, 3, 4-fields	16
1 direct field	13
Brachytherapy	3
No of chemotherapy cycles (n=31)	
1	12
2	19
MMC dose per cycle (mg)	
Range	10–30
<20	16
20	6
>20	9

formed. This was administered either through a direct perineal field delivering a dose of 15–23 Gy at a depth of 3 or 4 cm (13 patients), or through two, three or four-wedged fields technique, encompassing the anus and the perirectal area (16 patients). Eleven patients were boosted in the lithotomy position and in three patients intraluminary brachytherapy was applied to boost the primary tumor. The boost of 10–25 Gy to the involved inquinal nodes was used in three patients.

Chemotherapy. Treatment plan included two cycles of chemotherapy consisting of MMC 10–15 mg/m^2 day 1 and 5-FU 400–750 mg/m^2 over 4 or 5 days, delivered concomitantly with irradiation. The first cycle initiation was planned on day 1 of the irradiation, and the second – during the first week of the second part of irradiation. 5-FU was administered as a 4-hour infusion with the exception of five cases given continuous infusion. Of those three received a dose of 320 mg for 10 consecutive days and two 1250 mg for 5 consecutive days.

Two cycles of chemotherapy were administered in 19 patients and one cycle – in 12. Omitting the second cycle in seven patients was related to severe toxicity occurring after the first chemotherapy cycle.

Toxicity. The RTOG/EORTC acute radiation morbidity scoring criteria were used to assess treatment toxicity [3].

Results

Complete tumor remission (CR) was obtained in 26 patients (76%) including 25 patients with anal canal and one patient with anal margin cancer. All complete responders received chemo-radiation. In seven patients with anal canal cancer CR was confirmed by biopsy performed 4 to 6 weeks following completion of therapy. Partial remission (PR) was observed in eight patients – in five treated with chemo-radiation and in three treated with radiation alone. Salvage abdomino-perineal resection was performed in four patients who failed therapy and in two with recurrent lesion. Of those managed with salvage surgery, at the time of this analysis (May 31, 2002) three patients were alive and free of disease. The loco-regional tumor recurrence was observed in four patients (12%), including three with anal canal cancer and one with anal margin cancer. Relapses occurred after 2, 10, 13, and 22 months after treatment completion and in two cases were successfully salvaged with surgery. Overall, local treatment failure was observed in 12 patients (35%) including nine with anal canal cancer and three with anal margin cancer. Three patients in this group presented with T_{1-2}, eight patients (66%) with T_3 tumor, and one with T_4. Five patients presented with N_{2-3} disease. Two patients developed distant (liver and lung) metastases.

The actuarial colostomy-free survival probability for the entire group of patients was 45% (95% CI, 25–64%); 63%

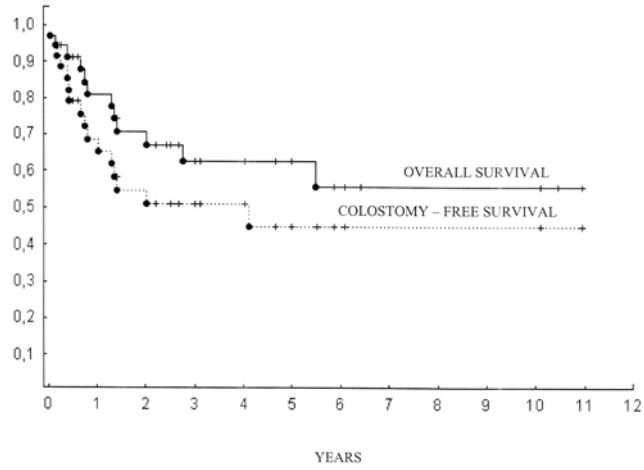

Figure 1. Overall and colostomy-free survival curves (Kaplan-Meier method).

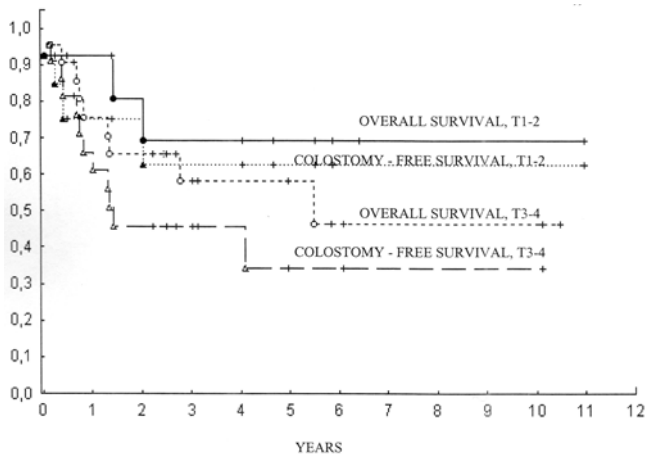

Figure 2. Overall and colostomy-free survival curves (Kaplan-Meier method).

(95% CI, 30–93%) in patients with T_{1-2} and 34% (95% CI, 9–60%) in patients with T_{3-4} tumors (Fig. 1, 2).

The gap of seven days between the first and the second part of irradiation was made in seven (25%) out of 28 patients who completed the split-course radiotherapy. Longer gap and/or unplanned treatment breaks caused by acute toxicity were performed in 21 out of these 29 patients (72%), and the six days gap in one.

Survival. At the final assessment (May 31, 2002), 23 patients (66%) were alive, all without evidence of disease. Ten patients died of progressive or recurrent disease and one of cancer-unrelated cause.

The actuarial 5-year overall survival (OS) in the entire group was 63% (95% CI, 45–81%) and the median survival has not been reached (Fig. 1). The actuarial 5-year OS was 69% (95% CI, 39–99%) for patients with $T_{1-2}N_0$ tumors and

58% (95% CI, 35–81%) for those with more advanced lesions (Fig. 2).

Toxicity. Nineteen patients (54%) experienced acute toxicity (Tab. 3). Fourteen patients (40%) experienced acute hematological toxicity; of those grade 3–4 neutropenia with accompanying infection occurred in nine cases (26%) and thrombopenia in seven (20%) – all in patients given combined therapy. There was one treatment-related death in a patient with neutropenia occurring after 20 Gy radiation therapy combined with the first cycle of chemotherapy (20 mg MMC day 1 and 750 mg 5-FU 4 h infusion given day 1 to 5). Gastrointestinal toxicity occurred in 13 patients (37%) and intense local cutaneous/mucosal reactions in five (15%).

Table 3. Acute toxicity (RTOG/EORTC scale)

Toxicity	Grade (n)			
	1	2	3	4
Leukopenia	1	3	4	5
Trombocytopenia	–	–	3	4
Anemia	1	2	–	–
Diarrhea	–	4	3	6
Vomiting	–	2	3	–
Skin/mucosal reactions	5	1	5	–

Late complications occurred in eight patients (24%) who completed therapy. They included lower extremity edema (one patient), bone fracture (hip and pubis, two patients), sexual dysfunction (two patients), and chronic diarrhea (two patients). Three patients (9%) reported insufficient sphincter function.

Discussion

In the present study actuarial overall and colostomy-free survival were 63% and 45%, respectively. Complete clinical tumor remission was achieved in 76% of cases. Not surprisingly, poorer response was obtained in patients with advanced disease. These results are similar to those reported by others [1, 4, 5, 8, 15, 21, 22, 24]. Complete remission of 80% for chemo-radiotherapy group, 54% for radiotherapy, 5-year survival of 56% for the whole patient group [1], and 3-year survival of 58% and 65% for radiotherapy and chemo-radiotherapy group, respectively [24], were reported in two randomized trials comparing concomitant radiotherapy and chemotherapy of 5-FU plus MMC and radiotherapy alone. Overall tumor control of 68% (56% with radiotherapy alone and 86% with irradiation combined with 5-FU and MMC) was reported in another larger non-randomized series of 192 patients with epidermoid anal cancer [5]. Myerson et al [15] in a series of 106 anal canal patients treated with radiation therapy alone or radiation combined with surgery or with chemotherapy demonstrated 5-year ultimate freedom from disease of 87% for T_1/T_2 N_0, 78% for T_3 N_0 and 43% (15% were salvaged with surgery) for T_4 N_0 or any N+. Sphincter conservation of 84% for T_1, 71% for T_2, 45% for T_3 and 43% for T_4 anal canal tumors managed with chemo-radiation using MMC and 5-FU, respectively were reported by Peiffert et al [19].

In our series local treatment failure defined as persistent or recurrent disease was seen predominantly in more advanced tumors. The stage, tumor size and nodal involvement have been demonstrated to be major prognostic factors in anal cancer [15,19]. The reported 5-year survival and local control rates are in the range of 80–90% and 80%, respectively for tumors less than 4 cm, and 50% and 40–50% for tumors larger than 4 cm. Less recognized is the prognostic impact of tumor location (anal canal vs. anal margin). Of the three anal margin patients in our series the cure was achieved in two but in both cases salvage surgery (abdomino-perineal resection or local excision of recurrent lesion) was performed. The third patient with huge ulcerative tumor died with uncontrolled local and distant disease.

The vast majority of patients in our series were treated with chemo-radiation and only a few received radiation therapy alone. The latter was administered almost exclusively to fragile elderly and immunosuppressed patients. Small number of patients applied radiotherapy does not allow comparison of treatment results in both groups. Non-surgical management of anal cancer by radiotherapy alone or combined with chemotherapy has yielded similar local control and survival rates in uncontrolled studies. However, two randomized trials demonstrated unquestionable benefit (significantly lower local failure rate) from chemotherapy added to irradiation [1, 24]. In consequence, in these studies patients managed with chemo-radiation were less frequently subjected to colostomy.

The chemo-radiation regimen using 5-FU and MMC is associated with substantial acute toxicity including deaths attributed to chemotherapy [1, 2, 4, 8, 24]. Myerson et al [15] observed acute toxicities including hematologic, chemotherapy extravasation, and stomatitis/esophagitis ($\pm$ enteritis)) in 14 (15%) out of 93 patients managed with chemo-radiation. In the series of Cummings et al [4] severe hematologic toxicity occurred in 28% of patients treated with split course radiation combined with 5-FU plus MMC. In our series 31% of patients experienced severe side effects, mainly hematologic, which in one case was fatal. Due to severe acute reactions the second chemotherapy cycle was administered in only 61% of patients. This frequent occurrence of hematologic toxicity might be partly related to relatively high MMC doses, with no reductions in elderly patients.

Apart from hematologic toxicity MMC can also cause other severe side effects such as lung toxicity, and hemato-

lytic-uremic syndrome. The role of MMC in the combined treatment schedule has been the subject of the randomized study of Radiation Therapy Group (RTOG)/Eastern Cooperative Oncology Group (ECOG) [8]. This study including 291 patients with T_{1-4} anal canal cancer compared radiation therapy (45 to 50.4 Gy) and 5-FU (1000 mg/m^2 intravenously per day for 96 h on weeks 1 and 4 of RT) with or without MMC (10 mg/m^2 per dose on day 1 of weeks 1 and 4, and total dose limited to 20 mg during each cycle). Both the overall and severe toxicity (including death related to neutropenic sepsis) was significantly greater in the MMC-5FU arm as compared to 5-FU arm (23% vs 7% grade 4 and 5 toxicity). However, MMC-treated patients experienced a significant reduction in colostomy rates (71% vs. 59%) and an increase in 4-year colostomy-free survival and disease-free survival. It was therefore concluded that despite greater toxicity, the use of MMC in a definitive radiation regimen for anal cancer is justified, particularly in patients with more advanced tumors.

5-FU, the other component of chemotherapy regimen is considered less toxic than MMC, however unusual sensitivity to 5-FU as a result of a disturbed fluorouracil clearance can not be excluded [13]. The potential benefit of replacing bolus injection of 5-FU by its continuous administration (during the entire irradiation period) remains to be established [20].

The increase in acute skin/mucosal acute reactions with chemo-radiation is established but generally accepted, primarily because these toxicities tend to be transient and self-limiting [12, 15].

In our series some patients experienced acute gastrointestinal toxicity probably related to relatively large irradiation fields. The volume of irradiated small bowel may be decreased by using prone position and by a four-field technique [15]. Importantly, it has been shown that doses of radiation that are normally well tolerated may cause substantial bowel injury when radiotherapy is combined with chemotherapy.

In an attempt to decrease toxicity of combined treatment for anal canal cancer patients a mitomycin-free regimen consisting of cisplatin (CDDP) and 5-FU has been a matter of clinical investigation [6, 10, 11, 14]. Whether the substitution of MMC by CDDP is associated with less toxic treatment remains unclear. In the study of Martenson et al [14] radiation therapy of 59.4 Gy with 2 week break after 36 Gy to the pelvis and groin combined with 2 cycles of CDDP (75 mg/m^2) and 5-FU (1000 mg/m^2 per day, for 4 days) resulted in an overall response and complete response rates of 95% and 79%, respectively, but still treatment was accompanied by substantial toxicity. In that study grade 3 or higher toxicities were seen in 15 out of 19 evaluable patients and one toxicity was lethal.

Other controversial issues of anal cancer treatment includes optimal fractionation schedule (protracted or split-course irradiation, the timing and duration of the rest period), the necessity of elective inquinal node irradiation, the way the boost to the primary lesion is delivered and the role of interstitial implants [10]. The common practice is administration of moderate doses of about 50 Gy, as the use of concurrent chemotherapy precludes the delivery of higher doses. On the other hand, doses of about 60 Gy have been reported to result in the increase of overall response rates up to 95% [14] and complete remission rate of 80% in patients with locally advanced anal cancer [1].

The elective irradiation for a clinically normal inguinal area makes the EBRT technique more complex and toxic. At our department elective groin irradiation is not routinely used, however this area is always irradiated in cases with involved or clinically suspected inquinal nodes. The inquinal node involvement in patients with early anal cancer is infrequent, except for tumors abutting or involving the anal margin or anal orifice. The overall nodal involvement increases up to 40–60% when the primary tumor is larger than 4 cm [2]. A careful evaluation of the perirectal lymph nodes as the main lymphatic spread in anal canal cancer is essential for a good staging of disease, however there is no agreement on the optimal imaging. Two most frequently used options include computed tomography or endorectal sonography [11].

In several cancers tumor repopulation during protracted radiotherapy is considered to be an adverse factor for treatment outcome. Consequently, shortening of the overall treatment time and avoiding unplanned treatment breaks should be attempted [7, 9]. For anal canal the more protracted schedule has been allowed and split-course radiation with a gap of various duration (one to eight weeks) was frequently used. In this schedule, the first part of irradiation included the dose of 30–45 Gy involving a substantial volume of the pelvis, and the second part constituted the local boost [1, 14, 19]. This strategy is related to the known slow regression of anal cancer and the need to recover acute normal tissue reactions. These sequele include in particular the perineal skin reactions which usually occur after 4 weeks of irradiation. The exact duration of this gap is not well established. One week treatment break after the first 30 Gy of radiotherapy, as initially planned in the regimen adopted in our institution, was possible in only a few cases, and this was mainly due to acute toxicity.

The frequency and intensity of late effects generally do not limit the use of chemo-radiation in anal cancer, however, eight severe (RTOG grade 3–5) late complications were observed [8]. The most common late sequele is chronic diarrhea [12], also local complications including soft tissue necrosis and rectal bleeding [19]. Major complications requiring colostomy or abdomino-perineal resection were seen in 7.5% of patients treated for anal cancer [21]. In our series 24% of patients experienced late effects but they were typically mild and not affecting quality of life.

Interestingly, anal canal cancer patients are at increased risk for additional malignancies, either preceding or following the anal tumor diagnosis. Because of the occurrence of additional malignancy it is postulated that patients with anal cancer should receive general oncologic screening in long-term follow-up [15]. In our series two patients presented with chronic leukemia.

Preservation of the anal function appears to be an obvious benefit achieved by conservative treatment for anal cancer patients. In our series, similarly to that of GERARD et al [11], 9% of patients reported unsatisfactory sphincter function after therapy. However, in a study of VORDERMARK et al [26], manometry determined complete sphincter continence was detected only in 56% of patients.

In conclusion, the results of this analysis remain in accordance with the literature data. The chemo-radiation using MMC and 5-FU allows for anal preservation in relatively high proportion of patients, however, this therapy is accompanied by the relatively high rate of acute severe toxicity. In view of the recent studies, the combination of 5-FU and CDDP in combination with radiotherapy should be considered, yet its efficacy remains to be determined in randomized studies.

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