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Original research article

Radiochemotherapy in Anal Cancer: cCR, clinical outcomes and quality of life using two different treatment schedules

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ABSTRACT

Aim: Main endpoint was a response rate to therapy; secondary endpoints were disease-free survival, overall survival, acute and late toxicities, specially in terms of anorectal and urinary continence.

Background: Radiochemotherapy for anal cancer achieves a good clinical response, locoregional control, anal function preservation. However, oncologic outcomes can differ using radiotherapy plus fluorouracil and mytomicin vs. cisplatin and fluorouracil.

Methods: Between 2000 and 2012, 27 anal cancer patients receiving radiotherapy combined with two different radiochemotherapy schedules, fluorouracil and mytomicin (group A) and cisplatin plus fluorouracil (group B). The Kaplan–Meier method was also used to estimate local control, overall survival and disease free survival. Statistical significance between curves was evaluated using the Log-rank test.

Results: Complete pathological response was found in 85.2% of patients, with higher rates of response in the group A (100% vs. 63.6%, $p = 0.039$). No significantly difference was found between the two groups for the other endpoints. Low rates of both acute and late toxicities were recorded.

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Conclusion: Radiotherapy plus fluorouracil and mytomicin provide a better complete pathological response than radiotherapy plus cisplatin and fluorouracil and a greater rate of anal sphincter function preservation. Globally, radiochemotherapy of the anal cancer provides excellent clinical outcomes with a good profile of acute and late toxicity, without difference between the two groups studied.

1. Background

Anal cancers represent 2–4% of all colorectal and anal tumors, showing an increased incidence over the last two decades due to the greater spread of human papilloma virus and human immunodeficiency virus.[1–7]

Combined chemo-radiation with sphincter preservation represented a shift paradigm in the treatment of anal cancer permitting to avoid abdominoperineal resection (APR) with permanent colostomy.

To date, combined chemo-radiotherapy represents a standard treatment for anal cancer.[8–10] Several series and prospective trials established the use of concurrent fluorouracil (5-FU)-mitomycin (MMC) plus radiotherapy (RT) as a standard primary therapy.[11–13] Other chemo-radiotherapy schedules have been investigated to reduce toxicity related to mitomycin infusion; the role of cisplatin (CDDP) has been studied in a variety of randomized trials such as feasibility, toxicity, and efficacy of capecitabine have been evaluated in phase II trials.[13–18]

Recently, the results of the largest anal cancer randomized trial showed that 5-FU and MMC associated with RT should remain a standard practice, because none of the investigated strategies seems more effective than standard treatment.[13–19]

Furthermore, it has recently been shown that the optimal time to assess a complete clinical response is 26 weeks after the end of chemo-radiotherapy. This could be ascribed to the long clearance of the anal cancer contributing to a later exhaustion of the response to treatment.[13,20]

Aim of our retrospective study was to evaluate long-term oncologic outcomes after concurrent chemo-radiation in patients with anal canal carcinoma receiving fluorouracil and mytomicin plus radiotherapy (FUMIR schedule, group A) vs. cisplatin and fluorouracil plus radiotherapy (PLAFUR schedule, group B). The main endpoint was a response rate to therapy. Secondary endpoints were disease-free survival (DFS), overall survival (OS), acute and late toxicities, especially in terms of ano-rectal and urinary continence.

2. Materials and methods

From 2000 to 2012, 35 consecutive patients affected by anal canal carcinoma, without distant metastases, were treated at our institution with curative chemo-radiotherapy.

2.1. *Pre-treatment assessment*

General clinical examination, blood tests, chest radiography, abdomino-pelvic computed tomography (CT) and magnetic resonance imaging (MRI) of the pelvis were performed for all cases. Loco-regional extent of the disease was evaluated with anorectal examination and rectoscopy; fine needle aspiration or biopsy were performed when inguinal lymph node involvement was suspected.

Clinical tumor staging was established according to the American Joint Committee on Cancer/International Union Against Cancer 7th edition tumor-node-metastasis (UICC-TNM) staging criteria.[21] Performance status was classified using the Eastern Cooperative Oncology Group (ECOG) performance score.[22]

2.2. *Chemo-radiotherapy*

A planning-CT of the pelvis district without intravenous or oral contrast was performed using a standard supine set-up. Axial CT images of 5 mm thickness at 5-mm intervals were obtained. A field of view (FOV) adapted to the patient and planned to include the patient contour, a 512-square matrix, and a standard reconstruction algorithm were used.

In all cases, the pelvis clinical target volume (CTV) was defined as: anal canal, perirectal nodes, external and internal iliac nodes, obturator nodes and inguinal nodes; to obtain the planning target volume (PTV), an additional margin of 1 cm in all directions was applied to the CTV. Boost included entire initial tumor and positive lymph nodes. Femoral heads, bladder and bowel were contoured as organs at risk (OARs). Irradiation was performed using 6 or 15 MV X-ray.

Radiotherapy treatment consisted in whole-pelvic 3D-conformal radiotherapy (3D-CRT); all patients received daily doses of 1.8–2 Gy, 5 days/week, for a total dose of 45–50 Gy to the 95% of the PTV. Patients treated between 2000 and 2010 were submitted to biopsy at the 6th week after the end of CRT, receiving a boost of 9–12 Gy (for a total dose of 54–59 Gy) when pathological complete response was achieved, while patients with residual disease at biopsy were referred to salvage surgery. Since 2011, a sequential boost was administered for a total dose of 54–59 Gy after pelvic irradiation.

Patients received radiotherapy combined with two different chemotherapy schedules: MMC 10 mg/m^2 on day 1 and 5-FU 1000 mg/m^2 in 96-h continuous infusion during weeks 1 and 5 of RT (FUMIR schedule, group A); cisplatin 60 mg/m^2 on days 1 and 29 and 5FU 1000 mg/m^2 per day on days 1–4 and 29–32 (PLAFUR schedule, group B).

2.3. *Response assessment*

Tumor response was assessed by anorectal examination, rectoscopy, CT and MRI imaging. Since 2011, patients not

achieving a pathological complete response were evaluated between the 10th and 13th weeks after completion of CRT to verify the tumor regression, stability, or progression of the disease.

Acute toxicity was graded by Radiation Therapy Oncology Group (RTOG) scoring criteria.[23] Late urinary toxicities were graded using CTCAE version 4.0 scale.[24]

The St. Mark's incontinence score was used to evaluate the occurrence and degree of fecal incontinence; this score is a measure of fecal incontinence based on the type (gas, liquid, solid) and frequency of anal incontinence, the impact on daily life, the use of pad, the need of constipation medication, and the presence of surgery.[25]

Additionally, basing on a validated Fecal Incontinence Quality of Life (FIQL) Scale questionnaire, a specific institutional FIQL questionnaire was administered in order to establish the impact of fecal incontinence on the quality of life in these patients. Four main aspects of life were examined: lifestyle, behavior, depression/self-perception and embarrassment.[26]

Both main and secondary endpoints considered were comparatively evaluated between patients receiving fluoropyrimidin and mytomicin plus radiotherapy (FUMIR schedule, group A) vs. cisplatin and fluorouracil plus radiotherapy (PLAFUR schedule, group B).

2.4. *Statistical analyses*

All qualitative variables were summarized as frequency and percentage and all quantitative variables as mean and standard deviation. The Kaplan–Meier method was used to calculate the 36 months and 60 months rates and relative standard error of Local Recurrence (LR), free survival, Disease Free Survival (DFS) and Overall Survival (OS). The follow-up was defined as the time interval between the start of radiotherapy treatment and death due to disease or as the time between the start of radiotherapy treatment and the first verified event. In patients in whom none of the events occurred, the observational time interval was defined as the period from the start of radiotherapy treatment to the last follow-up visit. The Kaplan–Meier method was used also to estimate OS, DFS and LR rate at 60 months of follow-up, after stratifying patients by patient characteristics. Statistical significance between curves was evaluated using the Log-rank test.

A p value of 0.05 or less was considered statistically significant. All statistical analysis was performed using SPSS® software 11.0 (SPSS Inc, Chicago, IL, USA).

3. Results

At the time of analysis of 35 patients treated, only 27 patients were evaluable (4 patients experienced a systemic progression of the disease during CRT and 4 patients were lost in follow-up). Of these 27 patients, 11 (40.7%) patients received chemo-radiotherapy based on platinum and fluorouracil (PLAFUR schedule, group B), while 16 (59.3%) mitomycin and fluorouracil (FUMIR schedule, group A).

Mean age was 65.1 years (SD ±11.8; range 44–83), with a predominance of women (70.0%).

Table 1 – Baseline characteristics of patients with anal cancer.

Characteristic	
Age (yr), mean ± SD°	65.1 ± 11.8
Gender, n(%)	
Male	8 (29.6)
Female	19 (70.4)
Histologic features, n(%)	
Adenocarcinoma	5 (18.5)
Epidermoidale	22 (81.5)
Grading, n(%)	
G1	2 (7.4)
G2	6 (22.3)
G3	2 (7.4)
Unknown	17 (62.9)
Type of chemotherapy, n(%)	
Plafur*	11 (40.7)
Fumir**	16 (59.3)
Clinical T stage, n(%)	
T1-T2	15 (55.5)
T3-T4	12 (44.4)
Clinical N stage, n(%)	
Negative	17 (63.0)
Positive	10 (37.0)

° SD: Standard deviation.
* Plafur: Radiotherapy plus cisplatin and fluorouracil.
** Fumir: Radiotherapy plus fluorouracil and mytomicin.

Twenty-two patients (81.5%) had performance status (ECOG score) 0 and 5 patients had an ECOG score 1(18.5%).

According to UICC-TNM (7th edition) staging classification, the clinical stage distribution of the patients was as follows: 3 patients (11.1%) in stage I, 11 (40.7%) in stage II, 4 patients (14.8%) in stage IIIA and 9 patients (33.4%) in stage IIIB. Twenty-two patients (81.5%) had histologically confirmed anal invasive squamous cell carcinoma, and 5 patients (18.5%) presented an adenocarcinoma histotype (2 in group A and 4 in group B; $p = 0.641$). Baseline characteristics of patients were summarized in Table 1.

The median follow-up time for all patients was 49 months (range 12–139 months) for all patients, 34 months (range 12–66 months) for group A and 75 months (range 21–139 months) for group B, starting the FUMIR scheduled most recently with respect to PLAFUR schedule.

Complete clinical response (cCR) was found in 23 patients (85.2%). Patients without a complete response at biopsy (4 patients, 14.8%) underwent a salvage APR. In the FUMIR group (group A) 100% of cCR were observed, while 63.6% cCR were obtained in group B receiving PLAFUR (chi-squared test = 4.253; $p = 0.039$).

Four of the 23 patients (17.3%) who initially achieved complete response experienced loco-regional recurrence; among the patients not achieving a cCR, one patient was free of disease at time of analysis, while three patients died, one for local-regional recurrence, one for metastasis and one for gastric tumor (Table 2).

Globally, local relapse was observed in 5 patients (18.5%) with a local control rate of 79.5 ± 8.3%; DFS after 36 and 60 months were 70.6 ± 9.5% and 63.6 ± 10.8% months, respectively (Fig. 1).

Table 2 – Clinical outcomes at follow-up in 27 patients.

Clinical outcomes	
Follow-up (months), *median (range)*	49 (12–139)
cCR[*], *n (%)*	
cCR	23 (85.2)
Non-cCR	4 (14.8)
Overall survival rate (%)	
36 months	81.0 ± 8.6
60 months	73.6 ± 10.5
Local control rate (%)	
36 months	79.5 ± 8.3
60 months	79.5 ± 8.3
Disease free survival rate (%)	
36 months	70.6 ± 9.5
60 months	63.6 ± 10.8

* cCR: clinical complete response.

Overall survival after 36 and 60 months were 81.0 ± 8.6% and 73.6 ± 10.5%, respectively (Fig. 1). Globally, 5 patients died for disease progression (metastasis or locoregional recurrence) and 2 patients died for non-cancer-related causes. A comparative evaluation of these outcomes after 60 months in FUMIR (group A) and PLAFUR (group B) groups showed a local control rate of 77.4 ± 11.9% and 81.8 ± 11.6%, respectively. In the FUMIR group, OS and DFS were 80.0 ± 12.6% and 68.6 ± 13.5% months, respectively, while in the PLAFUR group OS and DFS were 72.7 ± 13.4% and 63.6 ± 14.5%, respectively (Fig. 2).

Univariate analysis showed that none of the considered factors significantly affects OS, DFS and LC with the exception of age which appears slightly significant with respect to the OS and histology in relation to DFS (Table 3). No significant difference was found between the FUMIR and PLAFUR groups in terms of OS, DFS and LR; although squamous tumors clearly prevail and no comparison is possible between the two groups, differences were not observed between the two histotypes.

Considering acute toxicity, 19 patients (70%) showed skin reactions but only two patients showed grade 3–4 toxicity (7.4%).

Intestinal acute toxicity was observed in 13 patients (48%), a grade 3–4 toxicity was recorded in 2 patients (7.4%). Urinary toxicity was found in 2 patients (7.4%) with dysuria G1. No grade 3–4 hematological toxicity was recorded (Table 4).

In the comparative analysis of FUMIR vs. PLAFUR (group A vs. B), only for the skin toxicity, a statistical significance was found ($p = 0.021$), with a more detrimental effect caused by the FUMIR schedule.

Regarding late side effects, one patient (3.7%) had a complete urinary incontinence, 5 patients (18.5%) an episodic urinary incontinence. The fecal continence evaluation in patients submitted to APR was excluded from the analysis as complete incontinence of anal sphincter occurred in only one patient (4.3%). Excluding patients submitted to APR, complete incontinence of anal sphincter, defined according to St. Mark's incontinence score, occurred in only one patient (4.3%). No significant impairment of the quality of life was recorded basing on the institutional FIQL questionnaire. No differences in relation to late side effect were found between patients receiving FUMIR or PLAFUR schedule (group A vs. group B).

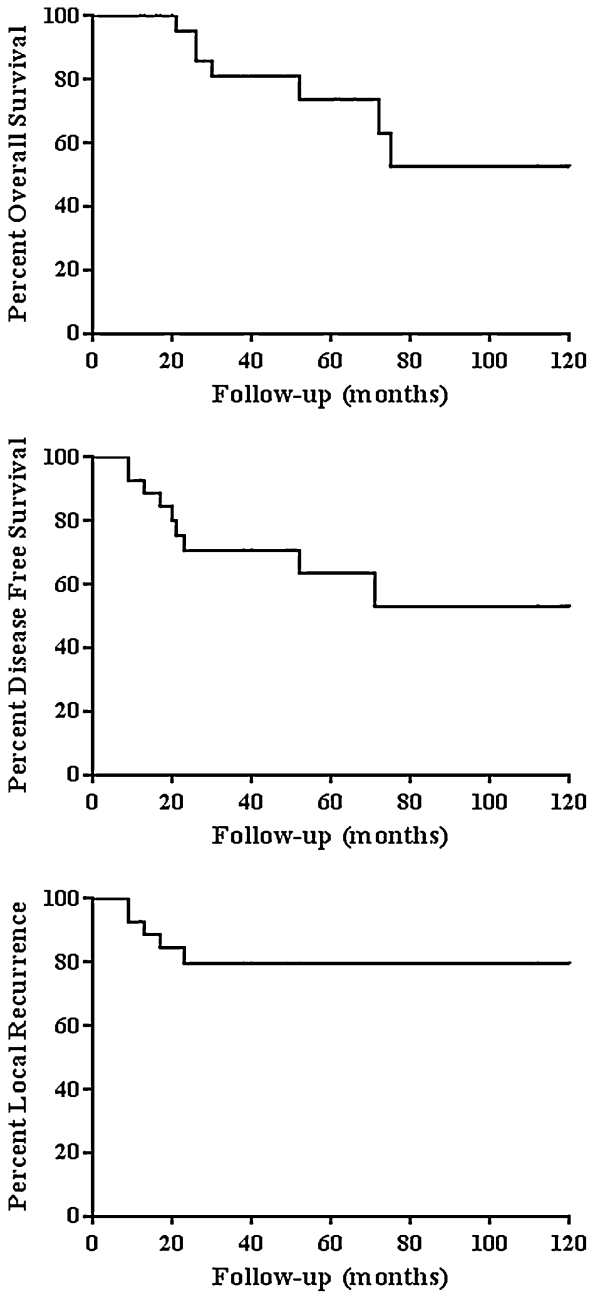

Fig. 1 – Curves of disease free survival, overall survival and local control for all anal cancer patients.

4. Discussion

In our study we retrospectively evaluated long-term outcomes after concurrent chemo-radiotherapy in patients with anal canal carcinoma in terms of response rate to therapy, LC, DFS, OS, and toxicity using two different treatment schedules (group A vs. group B).

Several series and prospective trials established the use of concurrent 5-FU-MMC plus radiotherapy as the standard therapy for anal canal carcinoma, reserving APR for salvage of locally persistent or recurrent disease.[27–30]

Table 3 – Univariate analysis.

Characteristic	Overall survival (%)	p-value	Disease free survival (%)	p-value	Local recurrence (%)	p-value
Overall	73.6 ± 10.5		63.6 ± 10.8		79.5 ± 8.3	
Age (yr)		0.041		0.147		0.586
≤69.0	87.5 ± 11.7		73.5 ± 13.9		85.7 ± 9.4	
>69.0	55.6 ± 16.6		52.9 ± 15.7		71.4 ± 14.4	
Gender		0.069		0.181		0.676
Male	60.0 ± 18.2		46.9 ± 18.7		72.9 ± 16.5	
Female	84.6 ± 10.0		75.9 ± 10.6		82.8 ± 9.1	
Histologic features		0.337		0.037		0.116
Adenocarcinoma	80.0 ± 17.9		40.0 ± 21.9		60.0 ± 21.9	
Epidermoidale	71.1 ± 12.8		68.5 ± 12.5		84.0 ± 8.6	
Clinical T stage		0.525		0.612		0.789
T1-T2	68.2 ± 15.8		55.2 ± 16.3		78.8 ± 11.0	
T3-T4	77.8 ± 13.9		70.0 ± 14.5		80.0 ± 12.6	
Clinical N stage		0.429		0.479		0.852
Negative	75.8 ± 12.7		64.4 ± 13.6		81.9 ± 9.5	
Positive	66.7 ± 19.2		59.3 ± 18.5		74.1 ± 16.1	
Type of chemotherapy		0.881		0.994		0.871
Plafur*	72.7 ± 13.4		63.6 ± 14.5		81.8 ± 11.6	
Fumir**	80.0 ± 12.6		68.6 ± 13.5		77.4 ± 11.9	
Clinical response (CR)		0.221		0.314		0.837
cCR°	82.4 ± 9.2		69.7 ± 10.5		80.5 ± 8.9	
Non-CR	50.0 ± 25.0		50.0 ± 25.0		75.0 ± 21.7	

° cCR: clinical Complete Response.
* Plafur: Radiotherapy plus cisplatin and fluorouracil.
** Fumir: Radiotherapy plus fluorouracil and mytomicin.

However, radiotherapy concurrent with 5-FU-MMC is affected by both hematologic and non-hematologic toxicity. To improve toxicity patterns of MMC, the role of cisplatin and other chemotherapy regimens has been widely investigated in a variety of recent randomized trials.[13,14,17,31] In a RTOG study 98–11, patients were randomized to receive RT plus concurrent infusion of 5-FU–MMC (group A, control group) or induction 5-FU- CDDP therapy followed by RT plus concurrent 5FU-CDDP therapy (group B, experimental group).[17] In this trial, no statistically significant difference in 5-year overall survival (75% vs. 70%, $p = 0.10$) or disease-free survival (60% vs. 54%, $p = 0.17$) was found between the two groups, while local-regional relapse rate was higher in the cisplatin-treatment group (33% vs. 25%; $p = 0.07$) and colostomy-free survival rate was higher in the MMC-treatment group (90% vs. 81%; $p = 0.02$). In this study, the rate of acute non-hematologic grade 3–4 toxicity was 74% while acute hematologic grade 3–4 toxicity was 61% in group A and 42% in group B.[17] Most recently, a long-term updated analysis of the previous study found a statistically significant difference between DFS and OS, with better outcomes for patients receiving 5FU-MMC (5 years DFS, 67.8% vs. 57.8%, $p = 0.006$ and 5 years OS, 78.3% and 70.7%, $p = 0.026$ for 5FU-MMC and CDDP-MMC, respectively).[32]

The ACT II study randomized 940 patients between four groups, to receive either MMC (12 mg/m^2 on day 1) or CDDP (60 mg/m^2 on days 1 and 29), with 5-FU (1000 mg/m^2 per day on days 1–4 and 29–32) and RT (50.4 Gy in 28 daily fractions); with or without two cycles of maintenance chemotherapy (5-FU and CDDP at weeks 11 and 14).[13]

The authors concluded that 5-FU–MMC with 50.4 Gy RT in 28 daily fractions should remain a standard practice, because neither strategy explored is more effective than a standard group (MMC-5FU based-CRT) in terms of complete response, progression-free survival or overall survival.[13]

Recently, Gleen-Jones and coworkers and ACT II study group showed that the optimal time to assess a complete clinical response is 26 weeks after the end of chemo-radiotherapy, rather than 6, 11 or 18 weeks. This could be ascribed to a long clearance of the anal cancer contributing to a later exhaustion of the response to treatment, a later surgical time and, potentially, a greater number of complete responses.[13,20]

In 2013, Kim and coworkers retrospectively evaluated long-term oncologic outcomes and risk factors for recurrence on 50 consecutive patients affected by anal cancer submitted to concurrent chemo-radiation treatment, during a median follow-up of 60 months.[8] They observed that after

Table 4 – Acute toxicity.

	Gastrointestinal	Genitourinary	Hematologic	Skin
G0	13 (48.1)	25 (92.6)	25 (92.6)	8 (29.6)
G1	3 (11.1)	2 (7.4)	1 (3.7)	2 (7.4)
G2	9 (33.3)	–	1 (3.7)	15 (55.6)
G3	1 (3.7)	–	–	1 (3.7)
G4	1 (3.7)	–	–	1 (3.7)

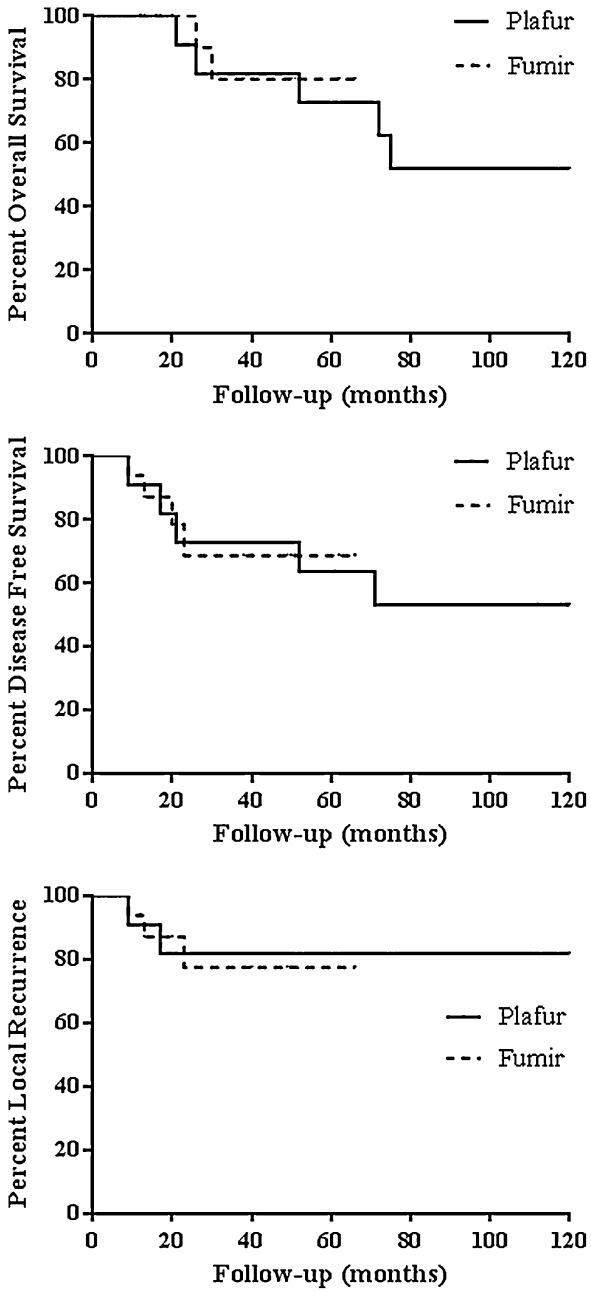

Fig. 2 – Curves of disease free survival, overall survival and local control for fumir and plafur groups.

5-year overall survival disease-free survival and loco-regional recurrence-free survival were 84.2%, 72.7%, and 69.9%, respectively. In this study, performance status and clinical complete response were reliable predictors of survival. In 2014, Russo and Ovalle, performed a retrospective analysis of 44 patients treated between 2002 and 2010. With a median follow-up of 56 months, with a minimum of at least 24 months, at 5 years the authors found both OS and DFS of 45%.[33]

In our study, we analyzed a population of 27 patients affected by anal carcinoma treated with primary radio-chemotherapy based on 5-FU associated with MMC or CDDP (FUMIR vs. PLAFUR schedules).

Globally, we obtained cCR in 23 patients (85.2%), in the FUMIR group (group A), 100% of cCR were observed, while 63.6% cCR were obtained in the group receiving PLAFUR (group B). We observed a LC rate of 79.5 ± 8.3%, a OS after 60 months of 73.6 ± 10.5% and a DFS after 60 months of 63.6 ± 10.8%. Although no significant difference was found between FUMIR and PLAFUR groups in terms of OS, DFS and LR, the rates of OS, DFS and LC in the two groups were quite different. Therefore, it is likely that a statistical significance could be achieved with a greater number of patients, but to date the size of the sample is too small to consider these results conclusive.

During treatment, grade 3–4 acute toxicity was recorded in only 4 (14.8%) patients. Regarding late-toxicity severe fecal or urinary incontinence were rare events, one case of a complete fecal incontinence and one of a complete urinary incontinence were observed.

Globally, the treatment was well tolerated and a good compliance was recorded, all patients completing the treatment. When comparing the FUMIR vs. PLAFUR schedule (group A vs. group B) we found a statistically significant difference only regarding skin toxicity, with a worse outcome in patients receiving FUMIR (group A). No statistical significance was found with respect to all other examined toxicity, both acute and late.

5. Conclusion

Although with an assessment of the response shorter than the latest evidence, our experiences confirmed that primary chemo-radiotherapy for anal cancer is effective on sphincter saving with a better rate of cCR for the FUMIR schedule and on other clinical outcomes evaluated without statistically significant differences between the two groups studied. Our study suffers from several limitations represented by the retrospective nature of analysis and the small size of the sample. However, of interest is the excellent result in terms of cCR and preservation of the sphincter function. An updated analysis with a greater number of patients considered is expected also to better evaluate if there are prognostic variables to predict long-term clinical outcomes.

Conflict of interest

None declared.

Financial disclosure

None declared.

Authors contribution

A - Study Design: Domenico Genovesi; B - Data Collection: Sara Di Santo, Antonietta Augurio, Annamaria Vinciguerra, Monica Di Tommaso; C - Statistical Analysis: Marta Di Nicola; D - Data Interpretation: Matteo Neri, Marta Di Nicola; E - Manuscript Preparation: Marianna Trignani, Sara Di Santo, Domenico Genovesi; F - Literature Search: Marianna Trignani, Lucia Anna Ursini, Angelo Di Pilla, Angelo Milano, Paolo Innocenti.

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