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The INCH Trial – Induction Chemotherapy in Patients With Bulky Anal Canal Cancer: Evaluation of the Pilot Phase

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Abstract. *Aim: To assess feasibility, complications and efficacy of induction chemotherapy followed by standard chemoradiotherapy in patients with bulky anal canal cancer. Patients and Methods: Patients with squamous cell carcinoma of the anal canal, staged bulky tumor with or without nodal involvement were prospectively enrolled. Before standard chemoradiotherapy, patients received induction chemotherapy with 3 cycles of 75 mg/m^2 cisplatin and 750 mg/m^2 5-fluorouracil. Patients were followed-up routinely until recurrence or death. Results: Seven patients with bulky anal canal cancer were evaluable for this pilot phase of the study. All patients had human papillomavirus-negative disease. Five completed the scheduled induction chemotherapy and all patients completed the programmed concomitant chemoradiotherapy. None had severe hematological toxicity. The majority of patients (6/7) had tumor downsizing after induction treatment. Six months after chemoradiotherapy, complete response was documented in three patients and salvage surgery was performed in two cases. With a median follow-up of 38 months (range=28-48 months), two patients are disease-free survivors. Conclusion: Induction chemotherapy has the potential to become a standard approach in patients with bulky human papillomavirus-negative anal canal cancer.*

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The optimal management of non-metastatic anal canal carcinoma is definitive chemoradiotherapy (1). Radical surgery consisting of abdomino-perineal resection (APR) is usually reserved for those with residual/recurrent local disease (1). Bulky anal canal tumor has a worse prognosis (<40% at 5 years) and its treatment should probably be more aggressive (2). Based on empirical data and on the efficacy demonstrated in patients with rectal cancer (3), induction chemotherapy may play a crucial role in cases of bulky primary anal canal cancer, favoring tumor down-sizing and early eradication of micrometastases, without affecting compliance with subsequent standard chemoradiotherapy.

The aim of the present single-center prospective study was to evaluate the feasibility and the clinical outcomes of induction chemotherapy followed by standard chemoradiotherapy (CRT) in patients with bulky anal canal carcinoma.

Patients and Methods

The INCH study is a research project coordinated by the Department of Radiological Sciences, Oncology and Pathology, Policlinico Umberto I, Sapienza University of Rome and was approved by the Sapienza University of Rome (RG120172B7970E08) (4).

Patient selection. Selection criteria included patients with newly diagnosed histologically proven squamous cell carcinoma of the anal canal, staged bulky tumor (T4 and ≥6 cm), with or without positive lymph nodes at diagnosis, without evidence of distant metastases; age ≥18 and ≤70 years; performance status ≤1; and adequate renal, hepatic and bone marrow function. Patients were excluded in the case of synchronous tumors, receipt of prior abdomino-pelvic radiotherapy, cardiovascular disease, history of neurological or psychiatric disorders.

Clinical examinations, including complete medical history and physical examination, as well as digital anorectal exploration,

Table I. *Patient and tumor characteristics. All patients were female and negative for human immunodeficiency virus and human papillomavirus.*

						TNM stage			Induction chemotherapy		RT, Gy	Concomitant chemotherapy	
ID	Age, years	PS	Histology	Grade	Tumor size (cm)	cT	cN	cM	Agent	Cycles		Agent	Cycles
1	68	0	SCC	3	7	4	1c	0	5-FU/Cisplatin	3	59.4	5-FU/MMC	2
2	72	1	SCC	2	6	3	0	0	5-FU/Cisplatin	2	54	5-FU/MMC	2
3	64	0	SCC	2	11	3	1a	0	5-FU/Cisplatin	2	68.4	5-FU/MMC	2
4	59	0	SCC	2	12	4	1c	0	5-FU/Cisplatin	3	65.4	5-FU/MMC	2
5	64	0	SCC	2	4	4	1c	0	5-FU/Cisplatin	3	59.4	5-FU/MMC	2
6	46	0	SCC	2	7.4	3	1c	0	5-FU/Cisplatin	3	59.4	5-FU/MMC	2
7	58	0	SCC	2	8	3	1a	0	5-FU/Cisplatin	3	59.4	5-FU/MMC	2

5-FU: 5-Fluorouracil; cM: clinical distant metastasis; cN: clinical node; cT: clinical tumor; ID: Identifier; MMC: mitomycin C; PS: Eastern Cooperative Oncology Group performance status; RT: radiotherapy; SCC: squamous cell carcinoma.

inguinal node palpation and anoscopic examination, were combined with radiological imaging to adequately assess local, regional nodal, and distant metastatic tumor [eighth edition of the TNM staging system (1)]. Radiological imaging consisted of transrectal ultrasound, total body contrast-enhanced computed tomography and diffusion-weight magnetic resonance imaging (DW-MRI) of the pelvis. Dihydropyrimidine dehydrogenase was tested in all patients and gynecological examination was performed in female patients.

Treatment strategy. All patients were treated with a multimodal treatment approach combining induction chemotherapy, followed by definitive CRT. Details of study design were described previously (4). Briefly, induction chemotherapy consisted of three cycles of the two-drug regimen: 75 mg/m^2 Cisplatin day 1 and 5-day continuous infusion of 750 mg/m^2 5-fluorouracil (5-FU) starting on day 1. Two weeks from the end of the last induction chemotherapy cycle, pelvic DW-MRI was performed to assess local clinical response. Independent of clinical response, standard CRT was started within 4 weeks of induction chemotherapy completion. The detailed CRT protocol has been described previously (5). RT was delivered with intensity modulate technique at a dose of 45 Gy (1.8 Gy/fr) to the whole pelvis plus 14.4 Gy (1.8 Gy/ fr) to the tumor volume with 6 to 15 MV energy photons. Concomitant chemotherapy consisted of mitomycin C (10 mg/m^2, days 1 and 29) and 5-FU (1000 mg/m^2/4 daily continuous infusion, days 1-4 and 29-32). During treatment, patients were followed-up weekly and up to 4 weeks after treatment. Toxicity scoring was performed using the Common Terminology Criteria for Adverse Events, Version 5.0 (6).

Follow-up. Following definitive CRT, patients were re-evaluated by serial digital anorectal exploration, inguinal node palpation and anoscopy at 6-week intervals. Patients with clinical suspicion of persistent disease at 6 months underwent a biopsy and consideration of APR was recommended (7). In cases of complete clinical response (cCR), the patient continued with a regular follow-up schedule, including complete physical examination and endoanal ultrasound at 3-monthly intervals for the additional 2 years and every 6 months for subsequent years. Pelvic DW-MRI was indicated in case of clinical suspicion of disease recurrence. Annual chest, abdominal, and pelvic computed tomography was performed for 3 years.

Outcomes. Evaluation of the pilot phase of the INCH trial included treatment feasibility, complications and efficacy prior to performing the main study. The primary outcome of the INCH trial was the 6-month cCR rate. cCR was defined as the total disappearance of tumor with a normal anaI mucosa determined by both clinical and diagnostic examinations at 6 months. Secondary outcomes included adverse events and time-to-event endpoints. Overall survival (OS) and distant metastasis-free survival (DMFS) were calculated in months from the date of the end of CRT to the first event, including date of the last follow-up and death (OS) and first distant failure (DMFS). Local failure-free survival (FFS) and locoregional FFS were defined as the persistence, re-growth or recurrence in the primary tumor site and in regional lymph nodes after definitive CRT, respectively. Both local and locoregional FFS were calculated in months and were assessed 6 months after the end of CRT. Anal dysfunction-free survival (ADFS) was defined as the need for colostomy in the absence of disease occurring after CRT to manage excessive fecal discharge or incontinence. ADFS included responder patient data and was calculated in months from the date of the end of CRT to the colostomy formation or last follow-up or death.

Statistical analysis. Statistical analysis was performed using RStudio-0.98.1091 software (Boston, MA, USA). Standard descriptive statistics was used to evaluate the distribution of each factor. Continuous variables were reported as median and categorical variables as frequencies or percentages. OS, DMFS, local and locoregional, and ADFS were estimated using the Kaplan–Meier method.

Results

Patient and tumor characteristics. Between January 2014 and March 2018, seven patients were enrolled. All patients signed an informed consent before the initiation of therapy. All were female with a median age of 61.6 (range=46-72) years. None was infected with human immunodeficiency virus. At baseline, all patients had a performance status score ≤1. Most patients (n=5) referred local pain at presentation and had a temporary colostomy. All patients had squamous cell carcinoma of the

Table II. *Acute hematological and non-hematological toxicity.*

	Induction chemotherapy				Chemoradiotherapy			
Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Haematological								
Anemia	2	1	0	0	4	0	0	0
Leukopenia	0	0	0	0	0	0	0	0
Neutropenia	1	0	0	0	2	0	0	0
Thrombocytopenia	0	0	0	0	4	0	0	0
Non-hematological								
Creatinine increase	0	1	0	0	0	0	0	0
Dysuria	0	0	0	0	1	0	0	0
Proctitis	0	0	0	0	2	0	0	0
Abdominal pain	0	0	0	0	2	0	0	0
Diarrhea	0	0	0	0	5	0	0	0
Constipation	0	0	0	0	1	0	0	0
Dermatitis radiation	0	0	0	0	5	1	1	0
Vaginal infection	0	0	0	0	0	0	0	0

anal canal. All primary lesions were bulky tumor. The median maximum tumor size was 7.4 (range=4-12) cm. Six patients (85.7%) had positive regional lymph nodes at diagnosis. There was no evidence of human papillomavirus (HPV)-related disease. Details are listed in Table I.

Details of induction chemotherapy. All patients received induction chemotherapy according to the study design (4). None had dihydropyrimidine dehydrogenase deficiency. Five patients completed the scheduled three cycles of induction chemotherapy. Two patients received two cycles because of renal toxicity in one, and suspicion of local disease progression in the other, confirmed by DW-MRI. Overall, hematologicaI toxicity occurred in three patients, including grade 1 anemia (n=2), grade 2 anemia (n=1), and grade 1 neutropenia (n=1). Regarding non-hematological toxicity, the only significant side-effect was a grade 2 elevation of creatinine registered in one patient (Table II). Locoregional clinical response was assessed by pelvic DW-MRI 2 weeks after the last induction chemotherapy cycle. Downsizing was evident in all cases but one (Figure 1). The median maximum tumor diameter assessed at post-treatment pelvic DW-MRI was 4 cm (range=0.7-11 cm). In three patients, tumor had shrunk ≥50% of the original size.

Details of chemoradiotherapy treatment. Independent of clinical response to induction chemotherapy, all patients received and completed the programmed concomitant CRT. Two patients received an additional dose of 6 and 9 Gy, respectively, to the tumor lesion with 6-MeV energy electrons. Radiotherapy was interrupted for 3 days for acute toxicity in one patient. None stopped concomitant

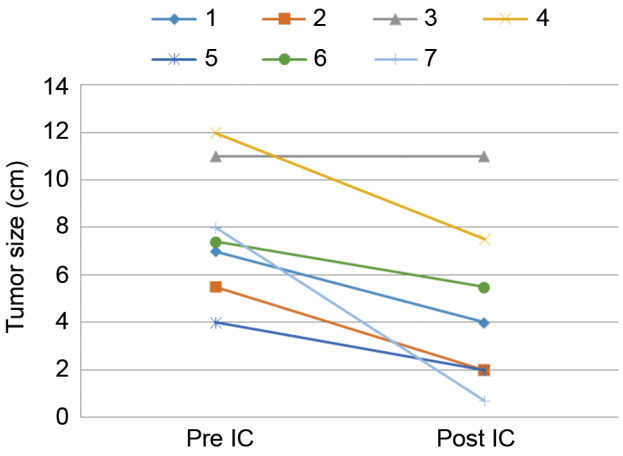

Figure 1. *Tumor size evaluation prior and after induction chemotherapy (IC) for individual patients.*

chemotherapy. Acute toxicity was mostly radiation dermatitis (n=7; 100%) and diarrhea (n=5; 71.4%). Details are listed in Table II. No severe hematological toxicity was recorded. One patient experienced severe radiation-related dermatitis. Local clinical response was assessed by clinical examination with digital anorectal examination 2 weeks after the end of chemoradiotherapy. A cCR occurred in two patients. The remaining five patients presented a clinical partial response.

Clinical outcomes. At definitive analysis of treatment response (6 months after treatment), we documented a cCR in three patients and a partial response in two. Stable disease

was noted in two patients and APR surgery was performed. Of these two patients, one had a good prognosis and was alive and disease-free at the time of analysis, whereas the other one experienced relapse distantly 2 months after surgery and died 10 months thereafter. Overall, there were five cancer-related deaths due to distant relapse with metastasis to the liver in one, abdominal lymph nodes in one, lung in two and bone in one. Of the two patients alive, there was no evidence of locoregional recurrence and distant disease. The median follow-up was 38 (range=28-48) months. The 2-year OS, DMFS, local and locoregional FFS were 57.1% [95% confidence interval (CI)=0.172-0.837], 28.6% (95% CI=0.041-0.612), 28.6% (95% CI=0.041-0.612) and 21.4% (95% CI=0.012-0.586), respectively. None needed colostomy to manage excessive fecal discharge or incontinence.

Discussion

The INCH trial supported induction chemotherapy in patients with bulky anal canal carcinoma. We demonstrated high treatment compliance, satisfactory treatment tolerance and a good response rate after induction chemotherapy. All patients completed the programmed standard CRT without dose reduction in terms of both radiation and concomitant drugs. There was no evidence of severe hematological toxicity. These data compare well with results previously reported for definitive chemoradiotherapy (5), thus confirming the absolute low risk profile of this induction chemotherapy followed by standard treatment.

Several studies addressed the relevance of induction chemotherapy prior to definitive chemoradiation in anal canal cancer (9). The RTOG 98-11 phase III trial failed to show survival superiority for induction chemotherapy followed by CRT over standard of care (5-year OS: 70.7% *versus* 78.3%, p=0.026) (10). Similarly, the UNICANCER ACCORD 03 phase III trial did not find an advantage for induction chemotherapy in colostomy-free survival (CFS) in locally advanced anal canal carcinoma (5-year CFS 76.5% *versus* 75%, p=0.37) (11). Despite any proven benefit in CFS, it should be noted that in a subgroup analysis of that trial, induction chemotherapy did not have a negative impact on patient quality of life 2 months after treatment (12). One can argue whether these results are still representative of survival outcomes in patients with bulky disease. Actually, these published data showed that different groups of patients and different treatment components have been mixed together, in terms of disease stage at diagnosis (clinical T2-T4, tumor >4 cm/positive nodes), type of concurrent chemotherapy (cisplatin/5-FU, mitomycin C/5-FU), radiotherapy characteristics (spilt-course, standard) and primary end-point (OS, CFS). As expected, the lack of a clinical benefit for induction chemotherapy was not supported by those studies in which only patients with poor prognostic features were eligible (13, 14). For instance, the Cancer and Leukemia Group B 9281 phase II study enrolled patients with clinical T3-4 disease with or without nodal involvement (bulky nodes or bilateral nodes) and induction chemotherapy followed by CRT resulted in long-term disease control in 91.1% of cases (13). In another retrospective series, 11 patients with clinical T4 anal canal carcinoma received primary chemotherapy prior to CRT and presented a statistically significant better CFS in comparison to those 27 patients who did not (100% *versus* 38%, respectively) (14). In this context, our prospective INCH study has the potential to provide some useful information on the use of induction chemotherapy in a specific setting of patients, namely those with bulky anal canal cancer presenting to a radiation oncology referral center. Another important consideration is that all our patients had HPV-negative disease. In line with other squamous cell carcinoma, such as head and neck cancer, HPV status is also recognized in anal canal cancer as an independent prognostic factor for survival (8). This might allow selection of candidates for an intensified treatment regimen for this prognostically unfavorable group. Induction chemotherapy might be an alternative treatment regimen to pursue in patients with HPV-negative bulky carcinoma of the anal canal. Once the advantage of induction chemotherapy followed by standard CRT is stated, the subsequent step is in regards to the inclusion of this approach as part of the best treatment in this subset of patients. Data from the literature are lacking due to the inhomogeneous results over different groups and even inside the same population. To date, as far as we are aware, this is the first study of induction chemotherapy focusing on a selected and homogeneous population of patients with bulky anal canal cancer. Another strength of the INCH study is the unambiguous definitions of time-to-event endpoints, according to the recommendations of Glynne-Jones et al. (15). Because of the exploratory nature of this preliminary analysis, the number of included patients was certainly small and the study lacked the power to detect significant differences in both primary and secondary outcomes. Therefore, we were unable to conclude whether or not induction chemotherapy was linked to a better response. In addition, our patients received stage-adapted standard of care treatment. But it should be considered that at present, the landscape of clinical trials has shifted to immunotherapy, and programmed death 1/programmed death ligand-1 expression status has been investigated as a prognostic biomarker in different cancer entities, including anal canal carcinoma (16-18). In this context, the INCH approach is likely to be an 'old strategy' on the topic. Treatment personalization is certainly essential and treatment intensification should be encouraged in patients with bulky HPV-negative anal canal cancer whilst we await larger studies with a longer follow-up time.

Conclusion

Although a larger trial is needed to confirm our results, the INCH strategy was safe, with promising efficacy in the management of patients with bulky anal canal cancer.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

FDF, DM, VT designed and supervised the study. AF, FI, VM, GG, GTC, RDP, GC, CM, NB collected data. FDF and AF did the statistical analyses and wrote the draft, with revisions from the other Authors. All Authors approved final version.

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