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ORIGINAL REPORT

Induction Chemotherapy and Dose Intensification of the Radiation Boost in Locally Advanced Anal Canal Carcinoma: Final Analysis of the Randomized UNICANCER ACCORD 03 Trial

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ABSTRACT

Purpose
Concomitant radiochemotherapy (RCT) is the standard for locally advanced anal canal carcinoma (LAACC). Questions regarding the role of induction chemotherapy (ICT) and a higher radiation dose in LAACC are pending. Our trial was designed to determine whether dose escalation of the radiation boost or two cycles of ICT before concomitant RCT lead to an improvement in colostomy-free survival (CFS).

Patients and Methods
Patients with tumors ≥ 40 mm, or < 40 mm and N1-3M0 were randomly assigned to one of four treatment arms: (A) two ICT cycles (fluorouracil 800 mg/m^2/d intravenous [IV] infusion, days 1 through 4 and 29 to 32; and cisplatin 80 mg/m^2 IV, on days 1 and 29), RCT (45 Gy in 25 fractions over 5 weeks, fluorouracil and cisplatin during weeks 1 and 5), and standard-dose boost (SD; 15 Gy); (B) two ICT cycles, RCT, and high-dose boost (HD; 20-25 Gy); (C): RCT and SD boost (reference arm); and (D) RCT and HD boost.

Results
Two hundred eighty-three of 307 patients achieved full treatment. With a median follow-up period of 50 months, the 5-year CFS rates were 69.6%, 82.4%, 77.1%, and 72.7% in arms A, B, C, and D, respectively. Considering the 2 × 2 factorial analysis, the 5-year CFS was 76.5% versus 75.0% (P = .37) in groups A and B versus C and D, respectively (ICT effect), and 73.7% versus 77.8% in groups A and C versus B and D, respectively (RT-dose effect; P = .067).

Conclusion
Using CFS as our main end point, we did not find an advantage for either ICT or HD radiation boost in LAACC. Nevertheless, the results of the most treatment-intense arm B should prompt the design of further intensification studies.

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INTRODUCTION

The prognosis of locally advanced anal canal carcinomas (LAACC) remains moderate. Two randomized trials have demonstrated that the concomitant addition of fluorouracil (FU) and mitomycin C (MMC) chemotherapy (CT) to radiotherapy (RT) can benefit colostomy-free survival (CFS).[1,2] Despite this, the 2-year local recurrence and colostomy rates remain relatively high at 25% and 30%, respectively, and metachronous metastases were frequent, although frequently not isolated.[2] Hence, the therapeutic ratio of concomitant radiochemotherapy could potentially be increased by intensifying the RT dose, keeping in mind functional results and the risk of necrosis.

Because of the toxicity related to MMC and to the proven efficacy of cisplatin-based regimens in other squamous cell carcinomas (SCC), a phase II trial was previously designed to test the combination of FU and cisplatin in SCC of the anal canal. This trial used induction CT (ICT) followed by concomitant radiochemotherapy (RCT) and demonstrated good treatment tolerance and a high response rate after ICT, thereby partially providing the rationale for our current trial.[3]

The split-course therapeutic scheme for irradiation and moderate doses of FU were chosen, as was

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standard at the time.[4,5] The dose of the boost remains undefined in LAACC.[6,7]

The objective of this phase III study was to evaluate the benefit of cisplatin-fluorouracil–based ICT and that of a higher dose of RT (HDRT) on CFS in LAACC.

PATIENTS AND METHODS

Patient Eligibility

Eligible patients were age 18 to 80 years and had histologically proven untreated LAACC with tumors larger than 40 mm and/or involved pelvic or inguinal lymph nodes. HIV-positive patients were not excluded. Exclusion criteria were nonsquamous histologies, tumors with predominant skin involvement, previous malignancy treated within 5 years, metastasis, hemoglobin lower than 11g/100 mL, serum creatinine greater than 130 μmol/L, and any contraindication to FU. The study was approved by a national scientific review board and the Lorraine Committee of Ethics. Written informed consent was obtained from each patient. Pretreatment work-up included a physical examination, chest x-rays, abdominopelvic computed tomography scan and/or endorectal ultrasound, and complete blood tests. Temporary colostomies were permitted in cases of severe bleeding or pain and in patients at risk of developing a fistula, provided a reversal of the colostomy was expected.

Study Design

By means of a 2 × 2 factorial design, the aim of this four-arm prospective randomized trial was two-fold: to determine the benefit of two cycles of ICT before pelvic concomitant RCT and to test the effect of a higher dose for the radiation boost. The primary end point was CFS. Secondary end points were local control (LC), overall survival (OS), and cancer-specific survival.

The patients were randomly assigned to one of the following four treatment arms. Patients on arm A received two ICT cycles, pelvic RCT, and standard-dose (SD) boost. Arm B patients received two ICT cycles, pelvic RCT, and high-dose (HD) boost. Patients on arm C (reference arm) received up-front pelvic RCT and SD boost. And patients assigned to arm D of the study received up-front pelvic RCT and HD boost.

Treatment

ICT: Study arms A and B, weeks 1 to 8. ICT consisted of two cycles of FU 800 mg/m^2/d by continuous intravenous infusion days 1 through 4 and days 29 to 32 plus intravenous cisplatin 80 mg/m^2 on days 1 and 29. For patients experiencing neutropenia, thrombocytopenia, diarrhea, or mucositis, doses of FU were reduced by 25%, 50%, and 100% for WHO grades 2, 3, and 4, respectively. Cisplatin dose was decreased by 50% in patients whose serum creatinine levels were higher than 130 μmol/L or in patients with grade 2 to 4 peripheral neurotoxicities.

RCT: Weeks 9 to 13 in study arms A and B, weeks 1 to 5 in arms C and D. Cisplatin was administered on days 1 and 29 of RT treatment and FU infusion as described in the preceding paragraph. Pelvic external-beam irradiation (EBI) was started on the same day as CT, after the FU infusion began. The target was the anorectal region and the pelvic nodal areas and included the inguinal node areas if they were involved or if there was involvement of the anal margin and/or pelvic nodes. RT technique consisted of either a standard four-field box or an anterior-posterior field conformal technique. Field borders extended from L5-S1 to the perianal region and laterally to the pelvic brim or wider if inguinal areas were included. An extension of 3 cm was recommended between the gross tumor volume and the planned target volume. A dose of 45 Gy in 25 fractions was prescribed to the International Commission on Radiation Units point, using 6 to 25 MV x-rays (electrons for inguinal nodes).

Irradiation boost. Three weeks after RCT was completed, patients who responded to the treatment went on to receive an irradiation boost by either EBI (1.8 to 2.0 Gy fractions) or low-dose rate interstitial brachytherapy (BT; 192-Iridium). BT was reserved for tumors involving less than half of the anal circumference at diagnosis. In the SD boost treatment arms (A and C), 15 Gy of RT was prescribed. In the HD boost arms (B and D), dose was prescribed according to response: 25 Gy for a minor partial response (mPR; defined as a less than 80% reduction in the primary tumor volume) and 20 Gy for patients with a complete response (CR) or major partial response (MPR; defined as a reduction of $\geq$ 80%). The BT dose was prescribed to the 85% isodose of the mean central dose. An abdominoperineal resection (APR) was recommended in nonresponders (patients with no change or disease progression at the primary site after pelvic RCT).

Follow-Up and Data Assessment

Clinical response was evaluated according to WHO criteria after ICT, at the end of the RCT and 2 months after the boost. Follow-up consisted of clinical examination every 4 months to evaluate local control and late complications. Evaluation under anesthesia was reserved for patients requiring a biopsy to confirm recurrence versus late toxicity. Follow-up cross-sectional imaging was reserved for patients with suspicion of recurrent disease. Late toxicities were assessed using long-term radiation sequelae LENT-SOMA (late effect normal tissues somatic objective management analytic) classification scales.[8]

Statistical Considerations

The primary end point was CFS. A 2 × 2 factorial design compared ICT versus no ICT (arms A and B *v* C and D) and SD versus HD boost (A and C *v* B and D).

Two hundred eighty-eight patients were required to demonstrate a CFS increase at 2 years from 70% to 85% (risk $\alpha = 5\%$, $\beta = 10\%$; unilateral test) and 307 patients were accrued. Data quality was ensured through review by the Fédération Nationale des Centres de Lutte Contre le Cancer, statistical staff, and the chairperson. Analysis was performed on an intent-to-treat basis. Survival curves were estimated using the Kaplan-Meier method, from the date of first treatment.

CFS was based on the documented date of colostomy, defined as a definitive colostomy for progression, relapse, or complication at the time of analysis, and did not include patients who had undergone a colostomy which was eventually reversed. OS was measured regardless of the cause of death. Cancer-specific survival was measured using LAACC or treatment complication as causes of death. Tumor-free survival was measured from the time of documented CR until recurrence or death as a result of disease, using the Mantel-Byar model.[9] LC was defined as the absence of tumor at the anal canal or margin, low rectum, or vagina. Regional failures were defined as pelvic or inguinal relapses. Metastatic failures were defined as extrapelvic relapses. We reported the values calculated using a two-sided test.

RESULTS

Between January 1999 and March 2005, 307 patients were accrued at 20 hospitals (CONSORT diagram in Fig 1). A planned interim analysis by an independent data monitoring committee was carried out after the inclusion of 101 patients.[10] Baseline patient characteristics were well balanced regarding age, sex ratio, T-stage, tumor size, nodal involvement, and tumor differentiation (Table 1). Median follow-up was 50 months for all patients (range, 0 to 102) and 60 months for patients still alive at the time of analysis.

There were no major deviations of the protocol. One hundred forty-eight patients received ICT, 301 patients received pelvic RCT, and 283 received an irradiation boost by EBI or brachytherapy (156 and 127 patients, respectively). Treatment characteristics and compliance are presented in Table 2. Acute grade 3 to 4 toxicity was observed in 118 patients (Table 3). One to three toxic deaths occurred in each of the four arms (Fig 1). No patient required APR for acute toxicity during ICT or RCT.

During ICT, 93% and 95% of the cycles were administered at full dose in arms A and B, respectively. During RCT, 79% and 82% of the cycles of chemotherapy were administered in patients having received ICT (arms A and B, respectively) versus 94% and 98% in patients

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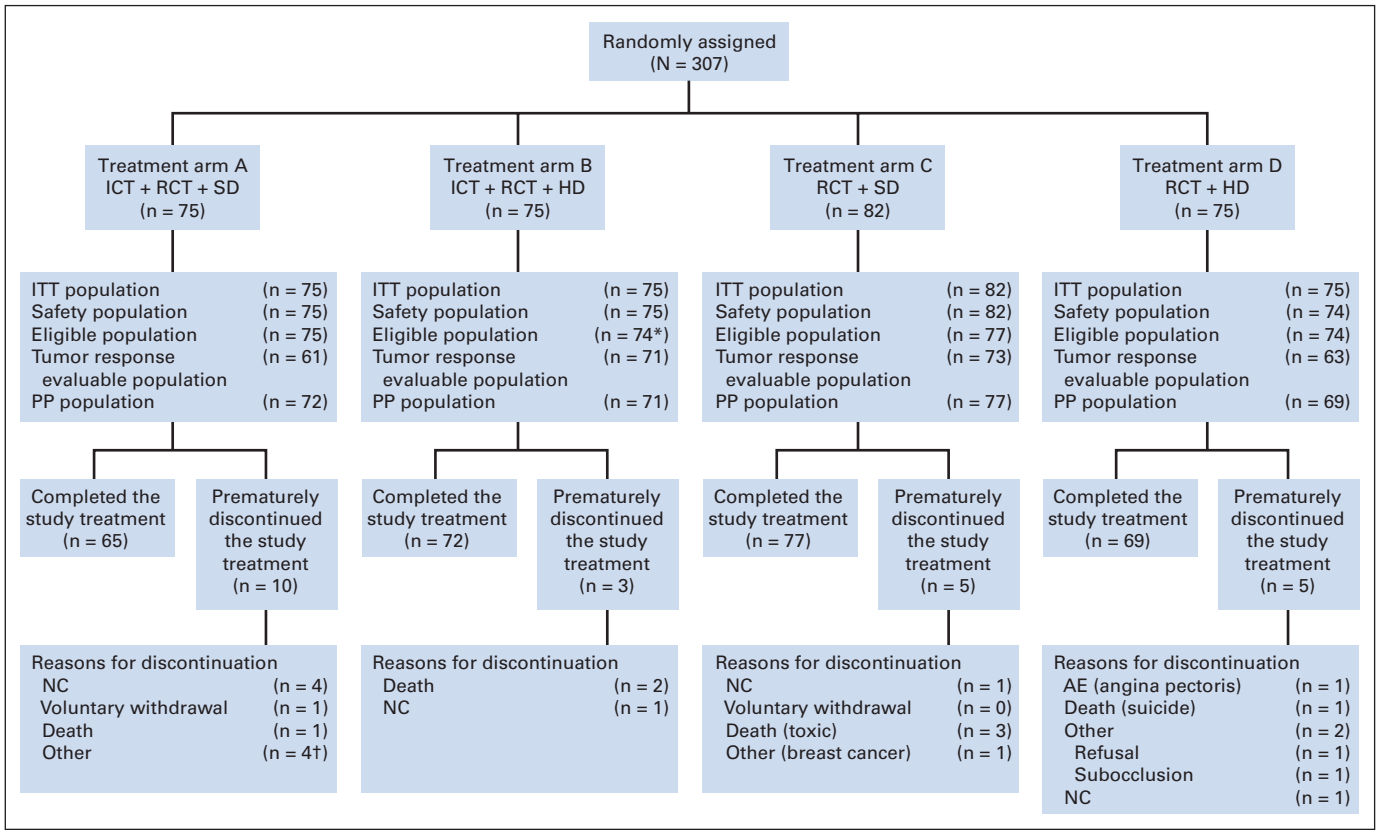

Fig 1. CONSORT diagram. AE, acute effect; HD, high-dose boost; ICT, induction chemotherapy; ITT, intent-to-treat; NC, no change; PP, per protocol; RCT, concomitant radiochemotherapy; SD, standard-dose boost. (*) No boost; (†) one major deviation, metastatic.

receiving up-front RCT (arms C and D, respectively). The number of cycles was well balanced in the SD versus HD radiation boost groups (87% *v* 85%).

Response was evaluated after each phase of treatment. Following ICT, response data were available in 60% of the patients; 11% had a CR and 60% a partial response. Following RCT and before the boost, response data were available in 82% and 84% of the patients of arms A plus B and C plus D, respectively. CR, MPR, and mPR for arms A plus B versus C plus D were 36% versus 28%, 42% versus 45%, and 19% versus 18%, respectively. Two months following the boost, 210 (79%)

Table 1. Patient Characteristics at Baseline

Characteristic	Arm A (n = 75)		Arm B (n = 75)		Arm C (n = 82)		Arm D (n = 75)		Total (N= 307)		*P**
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	
Age, years											.22
Mean	60		60		57.5		57.5		58.8		
Median	61		59		57.5		57				
Range	29-78		38-79		31-78		24-80		24-80		
Sex											.39
Men	12	16	11	14	18	21	18	24	59	19	
Women	63		64		64		57		248		
T1-T2/N0-N1	27/75	36	25/75	33	30/82	37	31/75	41	113/307	37	.62
Tumor diameter, mm											
Mean	41		45.9		45.4		45.2		44.4		
Range	15-80		15-90		10-99		10-99		10-99		
AB/CD									44/45		.30
AC/BD									43/46		.21
Node status											.86
N0-N1	57/75	76	60/75	80	61/82	74	57/75	76	235/307	76	
Poor differentiated	25/75	33	18/75	24	14/82	17	19/75	25	76/307	25	.13

*P value from the χ^2 test.

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Table 2. Treatment Characteristics

Characteristic	Arm A (n = 75)	Arm B (n = 75)	Arm C (n = 82)	Arm D (n = 75)	Total (N = 307)
No. of patients who had induction chemotherapy, n = 150					
1 cycle	75	73	0	0	148
2 cycles	70	71	0	0	141
Whole pelvis irradiation					
No. of patients	72	73	82	74	301
Total dose, Gy					
Median	45	45	45	45	45
Range	39.6-47.3	39.4-47.3	42.4-50.0	34.2-47.3	34.2-50
Days of treatment					
Median	35	36	35	35	35
Range	26-81	25-91	30-65	25-74	25-91
Chemotherapy during radiation, N = 307					
1 cycle	70	72	82	74	298
2 cycles	66	70	78	71	285
Abdoperineal resection after pelvis irradiation, No. of patients	4	1	1	1	7
Local boost					
No. of patients	66	74	75	69	
%	88	98	91	90	93
Median gap, days	24	26	24	24	25
Range	10-52	0-68	0-49	0-65	0-68
Brachy boost					
No. of patients	31	35	33	29	128
%	41	46	40	39	42
Median dose, Gy	15	20	15	20	
Range	14.5-22.4	11-25	11-25	3.6-27.4	
No. of patients with boost at 25 Gy	0	3	0	6	
External-beam tumor boost					
No. of patients	35	39	42	40	156
%	46	52	51	53	51
Median dose, Gy	15	20	15	20	
Range	4-19.8	6-26	13-23	14-25.2	
No. of patients with boost at 25 Gy	0	12	0	14	

Table 3. Acute Toxicity During ICT and RCT by Treatment Groups and Overall Late Toxicity (LENT SOMA classification)

Toxicity	Arms A and B Acute Toxicity		Arms C and D Acute Toxicity RCT	Overall Late Toxicity
	ICT	RCT		
Hematologic				
Grade 3	12	27	17	—
Grade 4	3	2	2	—
Diarrhea				
Grade 3	2	13	17	10
Grade 4	0	1	1	4
Infection				
Grade 3	1	2	2	—
Grade 4	0	0	1	—
Mucositis				
Grade 3	2	5	5	—
Grade 4	1	0	0	—
Cardiac				
Grade 3	1	1	0	—
Grade 4	0	0	1	—
Bleeding				
Grade 3	0	0	0	77
Grade 4	0	0	0	1
Anal pain				
Grade 3				26
Grade 4				12
Anal incontinence				
Grade 3				35
Grade 4				10
Ulceration/fistula				
Grade 3				21
Grade 4				16

ICT, induction chemotherapy; LENT-SOMA, late effect normal tissues somatic objective management analytic; RCT, concomitant radiochemotherapy.

of 267 evaluated patients achieved a CR and 36 patients (13%) achieved an MPR, resulting in 92% of all patients who could be kept in the sphincter preservation program (92%, 97%, 86%, and 94% for arms A, B, C, and D, respectively). No patient had APR for progressive disease before or during the pelvic RCT, whereas seven patients had APR for no change after pelvic RCT.

Eighty-eight patients relapsed. Most of the relapses were local, occurring in 53 patients at a median time of 13.5 months (range, 3 to 52). Thirty-three patients presented with isolated local relapse (Fig 2). Forty patients relapsed regionally and 20 relapsed with metastases. Twenty-three patients presented an overlap between local, regional, and metastatic failures. Late toxicities were mainly grade 1 or 2. Nine patients had grade 4 toxicities (necrosis, fistulae, bleeding, or pain), of whom five had an APR and four had a colostomy alone.

The actuarial 5-year results for the various end points of our study are presented in Figures 3 and 4. The 5-year CFS of groups A and B versus C and D was 76.5% versus 75% ($P = .37$) and of group A and C versus B and D was 74% versus 78% ($P = .067$). The 5-year OS for groups A and B versus C and D was 74.5% versus 71% ($P = .81$) and for groups A and C versus B and D was 71% versus 74% ($P = .43$).

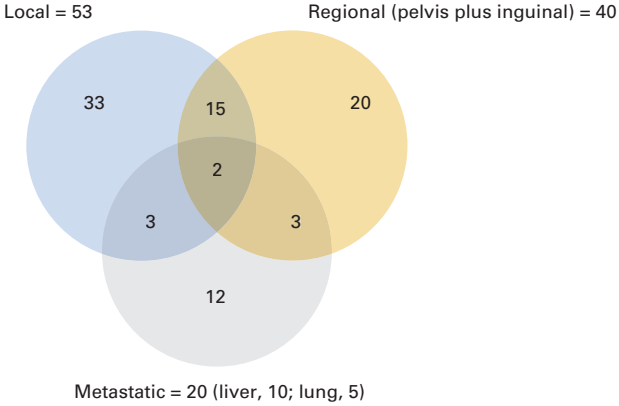

Fig 2. Distribution of the sites of treatment failure (n = 88).

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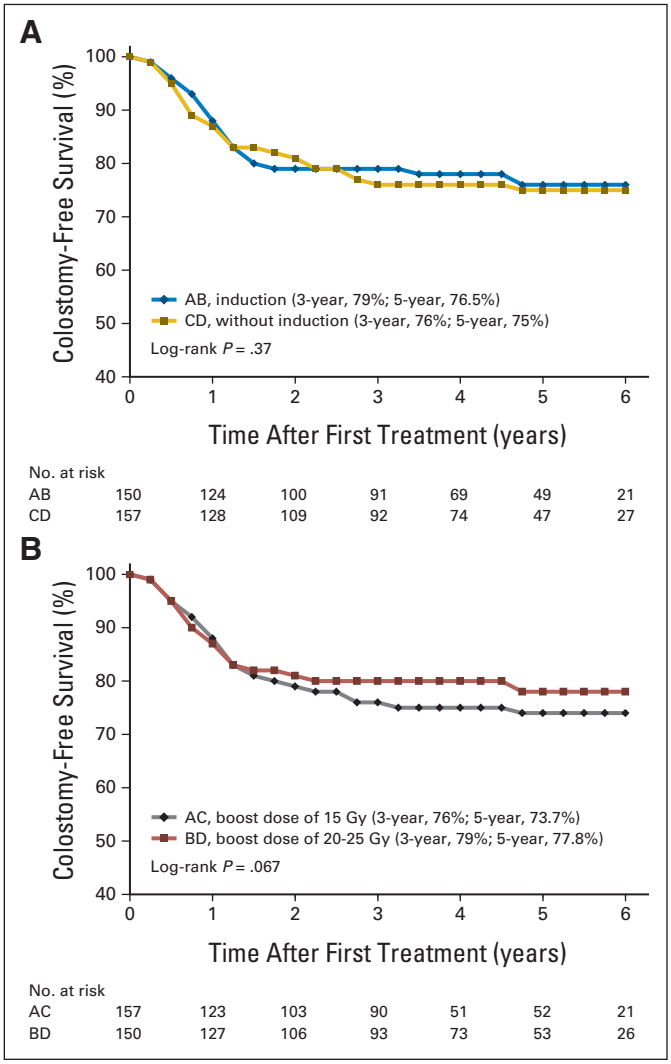

Fig 3. Actuarial colostomy-free survival. (A) Groups A+B versus groups C+D and (B) groups A+C versus groups B+D.

DISCUSSION

CFS was the most significant end point in the European Organisation for Research and Treatment of Cancer trial for LAACC,[1] a study that included a patient cohort and treatment schedule similar to our study. CFS reflects the combination of both LC and the absence of deleterious effects on the anal canal.

The aim of CT delivered concomitantly with RT is to increase locoregional control as a result of radiosensitization. This has been shown to be of benefit in LAACC in terms of CFS.[1] Given neoadjuvantly, CT may reduce tumor bulk before RCT, thereby improving oxygenation of both tumoral and normal tissues. This in turn may increase LC and reduce the rate of necrosis, resulting in higher sphincter preservation rates. This effect on organ preservation has been demonstrated in head and neck primaries, specifically with cisplatin-based ICT in pharyngolaryngeal tumors.[11,12] Conversely, ICT may contribute to local failure by increasing total treatment time, which may prove most deleterious in tumors that do not respond to the CT regimen. Finally, induction and concomitant CT may play a role in reducing metachronous metastases.

The use of ICT is, however, controversial for LAACC.[13,14,15] A previous phase II study[3] evaluated the role of ICT using cisplatin and FU in LAACC. CR and MPR rates were 10% and 51% after ICT, 67% and 28% after RCT, and 93% and 5% after treatment completion. The 3-year actuarial OS, CFS, and relapse-free survival rates were 86%, 73%, and 70%, respectively. These results were comparable with those of the European Organisation for Research and Treatment of Cancer trial[1] that comprised a similar patient population and used the same schedule of radiochemotherapy, but did not give CT neoadjuvantly and used MMC instead of cisplatin. In that trial, OS, CFS, and relapse-free survival rates at 3 years were 57%, 72%, and 68%, respectively. The encouraging results of the phase II study formed the rationale behind the use of ICT in arms A and B of our study. Of note, the cisplatin arm of Radiation Therapy Oncology Group (RTOG) 98-11study included a neoadjuvant component and showed no difference in disease-free survival or metastatic disease.

As for other SCC primaries, the combination of cisplatin and FU has been shown to be effective in SCC of the anal canal both in the recurrent[16-18] and neoadjuvant[19-21] settings, with objective response rates of 55% and 82%, respectively.

At the time of inception of the ACCORD 03 trial, cisplatin was preferred to MMC because of lower toxicity when given concomitantly with irradiation and high efficacy in anal canal carcinomas,[22-25] even when used as salvage therapy.[15] Since then, the RTOG 98-11 trial[26] has confirmed the superiority of the standard of concurrent FU-MMC and radiation over FU-cisplatin (induction and concurrent) and radiation, in terms of colostomy rates (19% *v* 10%; $P = .02$).

The dose of the irradiation boost is also controversial. Although 60 Gy or higher (including a boost of 15-20 Gy) was a standard dose in Europe in the 1990s, North American centers used total doses of 50 Gy or less and phase II trials of dose escalation were being conducted at the time.[6] We decided to evaluate two dose levels (15 Gy *v* 20-25 Gy) to determine whether a higher dose could result in better LC without added local toxicity, resulting in better CFS. The 25 Gy dose level was considered high risk for complications and was therefore only delivered in patients who exhibited an mPR after the RCT phase of treatment.

Our phase III trial, designed as a factorial 2×2 plan, could not demonstrate a benefit for neither ICT nor HDRT in patients with LAACC in terms of CFS. Nevertheless, treatment intensification in terms of CT and/or RT dose was not deleterious compared with the standard treatment (arm C). Dose escalation of the radiation boost (arms B and D) showed marginal evidence in CFS at 5 years and merits further investigation. Although this trial was not designed to make single arm comparisons, the results of the most intensified treatment arm (arm B) are encouraging, and combinations of induction therapy and radiation dose escalation should be explored further. Based on the discrepancy between tumor-free survival and local control in the induction arms (Fig 4) it is conceivable that cisplatin-based neoadjuvant chemotherapy has an effect on subclinical disease, given that significant responses of this regimen have been described in metastatic disease. However, because half of all recurrences are local, this potential impact of induction chemotherapy on subclinical disease is minimized.

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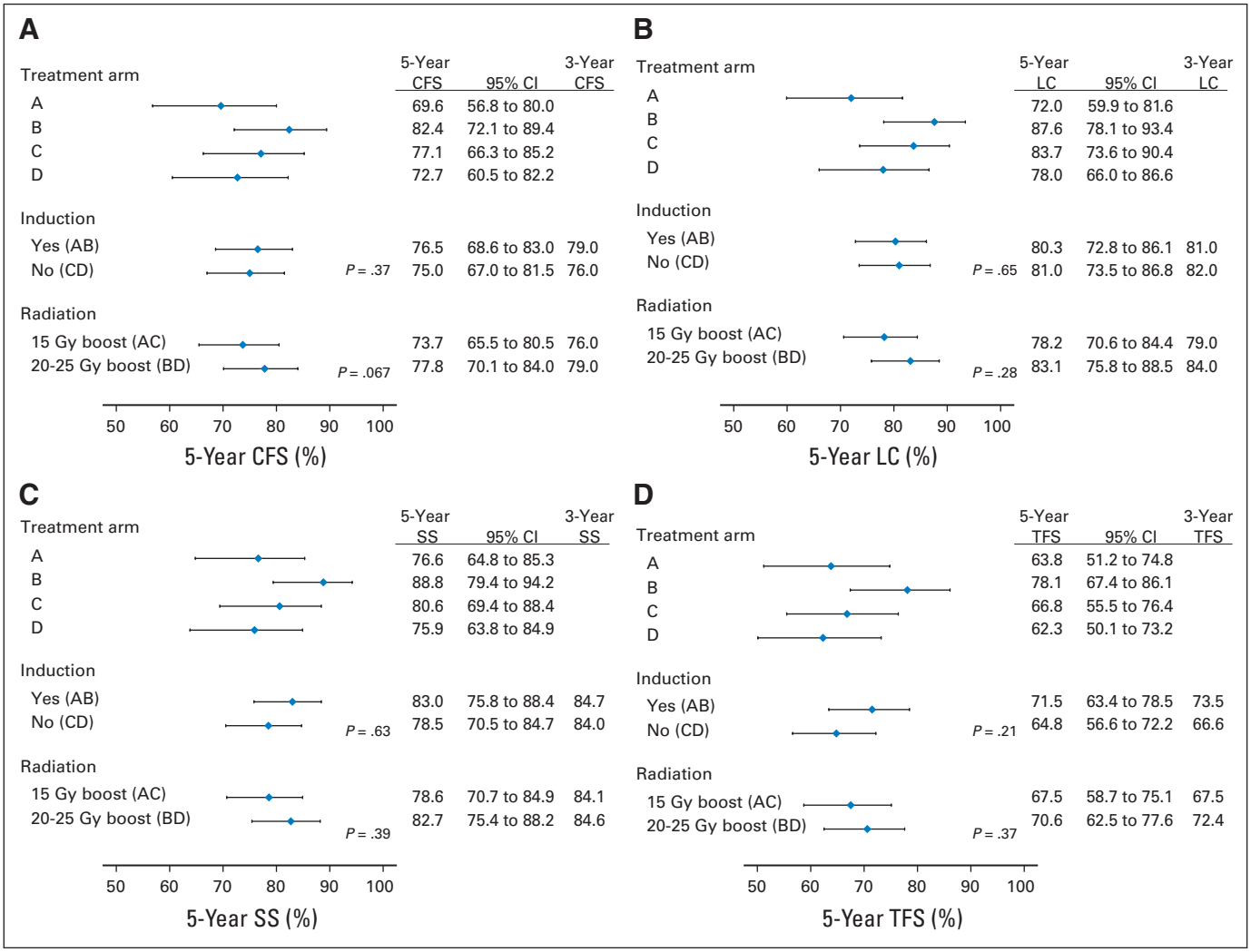

Fig 4. Actuarial 5-year results by percentage. (A) Colostomy-free survival (CFS); (B) local control (LC); (C) specific survival (SS); (D) tumor-free survival (TFS).

Our study has some limitations. CFS in reference arm C (SD radiation and no ICT) was higher than the 70% planned in the hypothesis of this trial. This may be as a result of several reasons, including an improvement in radiation techniques over time and better work-up of patients before treatment, perhaps resulting in stage migration. In addition, based on radiobiologic considerations, the protocol called for a reduction in the mandatory treatment break to 3 weeks, compared with 6 weeks in the previously mentioned phase II trial.[3] Moreover, 37% of patients included had earlier-stage disease (T1-2, N0-1, American Joint Committee on Cancer stage II), which could result in a lower probability of observing a statistically significant difference.

One can also argue that the boost doses chosen for our study were not sufficiently different to observe a statistically significant effect on local control and CFS, as few patients were administered therapy at the 25 Gy level. The use of BT as a boost was well balanced among the four treatment arms and therefore does not have a confounding effect.

Our study consisted generally of older patients, and the selected doses of chemotherapy were lower than those prescribed for patients with primary head and neck or esophagus cancer. Although rare during ICT (5% of the patients), toxicity-related dose reductions during RCT were necessary in 9% and 19% of the concomitant cycles in patients treated without and with ICT, respectively. Newer techniques of irradiation, such as IMRT, should reduce this toxicity by better sparing organs at risk, thereby preventing chemotherapy dose reductions and/or treatment interruptions.[27-29]

Although the small increase in CFS and LC with HDRT in this study did not reach statistical significance ($P = .067$), future trials should study this question further as local relapse remains the main site of failure. In RTOG 98-11, tumor diameter (≥ 5 cm) was the only independent pretreatment predictor of the 5-year colostomy rate.[30]

Future work should also examine dose effect as a function of tumor size. This will be conducted by our group to identify a subgroup of patients who may benefit from dose escalation and to investigate other radiotherapeutic approaches in patients with LAACC, such as treatment acceleration and IMRT. Use of the latter technique should make it more feasible to escalate boost doses and improve the hematologic and gastrointestinal tolerance. Preliminary results of RTOG 05-29 are encouraging.[31]

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The low rate of treatment-related colostomies in all four arms of our study opens the possibility to evaluate the concept of an integrated boost with concomitant chemotherapy, thereby delivering doses of 2.0 to 2.4 Gy/d to the primary tumor and involved nodal sites. We await the results of the ACT II trial[32] that will shed some light on the role of adjuvant platinum-based chemotherapy. Other combinations of systemic agents have demonstrated good tolerance and efficacy, including new targeted drugs such as cetuximab, and are under evaluation in phase II trials.[33,34]

Our trial could not demonstrate a benefit for ICT nor HD of radiation on CFS nor LC in LAACC. The low toxicity and high rate of LC, particularly for the most intensified arm B, suggests the possibility of further study of increases in dose-intensity, with new drugs, and new techniques of irradiation. Local relapse remains the predominant site of failure and the short interval between treatment and local relapse renders such trials more feasible.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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