Follow-up in a long-term randomized trial with neoadjuvant chemotherapy for squamous cell cervical carcinoma

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Summary

Objective: To assess the role of neoadjuvant chemotherapy to achieve radical surgery in a larger number of patients with locally advanced/or bulky Stage IB cervical carcinoma. We conducted a trial to determine whether neoadjuvant chemotherapy would improve disease-free survival and overall survival in Stage IB-III cervical cancer. *Design:* Prospective randomized clinical study with long-term follow-up. *Setting:* Department of Gynecology, Perinatology and Child Health, II Faculty University of Rome "La Sapienza". *Methods:* 288 patients with squamous cell carcinoma of the uterine cervix, FIGO Stage IB-IIIB were randomized to one of the following treatments: three courses of neoadjuvant chemotherapy with cisplatin, vincristine, bleomycin (NACT arm; n = 159); conventional surgery or exclusive radiotherapy (CONV arm; n = 129). There was no difference in age, FIGO stage, tumor size and lymph node involvement between the two groups (p = ns). Two hundred and thirty-four patients in Stage IB-IIb (n = 129 NACT arm and n = 105 CONV arm) and 24 patients in Stage III (NACT arm) who proved to be chemosensitive underwent radical hysterectomy. Six Stage III patients, non responders to chemotherapy, and 24 patients, Stage III of the CONV arm, underwent radiotherapy. Follow-up extended for seven years. *Results:* The study was performed on disease-free survival related to several prognostic factors: age, FIGO stage, tumor size, grading, parametrial involvement, lymph node status and surgical margins. Recurrence of disease occurred in 49 (32.1%) patients of the NACT arm (n = 153) and in 39 (37.1%). patients of the CONV arm (n = 105). Statistically significant differences in the recurrence of the disease were related to FIGO stage ($p < 003$), grading ($p < .05$), parametrial involvement ($p < .002$) lymph node status ($p < .0001$) and tumor size (p <.002). No statistical significance was related to age and surgical margins (p = ns). Disease-free and overall survival in the two groups were, respectively, 65.4% vs 53.5% (p = ns) and 70.4% 65.9% (p = ns)

Key words: Cervical cancer; Neoadjuvant chemotherapy; Radical hysterectomy.

Introduction

Although the early stages carcinoma of the uterine cervix have a high possibility of treatment aimed at a permanent cure, there is still no agreement on the best approach for locally advanced cervical cancer.

The prognosis of such disease has not improved despite the therapeutic advances since 1950 [1]. Several factors may contribute to treatment failure; the risk of recurrences is high in patients with unfavorable prognostic factors, such as lymph node involvement, tumor volume, positive parametrial specimens, high tumor-grading and invasion of the lymph-vascular spaces [2-4].

Neoadjuvant chemotherapy inducing elimination of micrometastasis and regression of cervical neoplasia made it possible to achieve radical operability. Chemotherapy was proposed during the eighties as a neoadjuvant regimen to increase the surgical operability of neoplasia classified unsuitable for surgery [5-14]. Whether the introduction of preoperative chemotherapy effectively improves the overall and/or disease-free survival is controversial [15-19]. In spite of the many therapeutic protocols for cervical carcinoma proposed during the past 50 years, survival has remained, substantially, almost unchanged [20]. Data on recurrence are available from three trials [21-23] in which the OR for recurrences is in favor of neoadjuvant chemotherapy, but the results are not statistically significant (p = .21). Neoadjuvant chemotherapy has, however, an undoubted biologic rationale because it represents an in vivo test of chemosensitivity that can influence subsequent therapeutic strategies [24].

Materials and Methods

Design

We conducted a prospective, randomized clinical study on 304 patients with histologically diagnosed squamous cell carcinoma of the uterine cervix in Stages IB-IIIB. The recruitment started January 1988 and ended December 2002 at the Institute of Gynecology and Obstetrics, University of Rome "La Sapienza". Inclusion criteria were: age less than 65 and absence of severe systemic pathologies or other neoplastic pathologies; exclusion criteria were: pre-existing neuropathies, leucopenia (< 4,000 mm^3), thrombocytopenia (< 100,000 mm^3), abnormal renal (serum creatinine > 1.5 mg/dl, creatinina clearance < 60 ml/min) and hepatic (bilirubinemia > 1.2 mg/dl) functions. Two hundred and eighty-eight patients were enrolled in the study, with a median age of 48.5 years (range 32-65 yers).

The clinical staging procedure was performed according to the International Federation of Gynecology and Obstetrics (FIGO, 1985): 189 patients were classified as Stage IB, 45 as Stage IIA and 54 as Stage IIIA-IIIB. To improve clinical staging, in addition to clinical examination, cystoscopy, rectosig-

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moidoscopy, computed tomography (CT) or magnetic resonance imaging (MRI) were performed in all patients.

Tumor size was evaluated by pelvic ultrasound and/or MRI: 168 patients showed tumor size of < 5 cm (58.3%), 120 patients (41.7%) tumor size of > 4 cm.

In addition, pelvic and/aortic lymph nodes were evaluated by lymphangiography or CT; neoplastic involvement of the pelvic and/or paraaortic nodes was diagnosed in 75 out of 288 patients.

Subsequently, patients were randomized by computer generated selection in two groups: 159 patients were given neoadjuvant chemotherapy (NACT arm) and 129 were the control group treated with conventional surgery or exclusive radiotherapy (CONV arm). Informed consent was obtained from the patients. The study was examined and approved by the Ethical Committee of this University.

Neoadjuvant chemotherapy and evaluation of tumor response

In the group that received neoadjuvant chemotherapy, a polychemotherapy regimen with cisplatin, vincristine, bleomycin (PVB) was used. A maximun of three cycles of neoadjuvant chemotherapy was administered at 21-day intervals according to the following sequence: cisplatin (P) 50 mg/m^2 (day +1), vincristine (V) 1 mg/m^2 (day +1) and bleomycin (B) 25 mg/m^2 (day +1 - +3). During treatment, patients were evaluated with hematochemical and instrumental tests, such as blood count, serum levels of creatinine, urea nitrogen, liver function, study of the respiratory function, and radiological pulmonary control. The toxicity of the chemotherapeutic drugs was evaluated according to the World Health Organization guidelines (WHO, 1979) [25]. Treatment was delayed one week if leukocytes were between 2,000 and 3,000 mm^3 and platelets were between 50000 and 100000 mm^3. If symptoms persisted for more than one week, vincristine was reduced to 50% of the normal dose, while the doses of bleomycin and cisplatin were not changed.

Clinical examination, colposcopy and pelvic ultrasound were used to evaluate the responsiveness to chemotherapy and therapeutic response was classified according to the WHO criteria [25].

Surgical procedure

Two hundred and thirty-four patients in Stage IB and IIB (n-129 NACT arm and n-105 CONV arm) underwent type III-IV radical hysterectomy according to Piver [26] with systematic lymph node dissection of the lumbar-aortic area as well as pelvic lymphadenectomy (modified radical hysterectomy according to Wertheim-Valle [27]. Furthermore, the group of patients undergoing surgical treatment was increased by 24 Stage IIIA-IIIB patients (NACT arm) reassessed and classified as suitable for radical surgery. Surgery was performed within four weeks of neoadjuvant chemotherapy.

A macroscopic evaluation was systematically made of the residual tumor as well as a histological study of the uterine cervix, parametria, paracolpos and all nodal tissue removed. The tumor grading was also evaluated.

Radiotherapy

Surgical treatment could not be performed on the patients classified as Stage III, in either the control group (n = 24) or non respondent patients treated by neoadjuvant chemotherapy (n = 6). In these cases, patients were randomized to radiotherapy: patients were initially treated with external-beam radiotherapy on the whole pelvis (50 Gy) over five to six weeks. Subsequently, the patients were treated by intracavitary brachytherapy with a maximum dose of 30 Gy (low-dose-rate; LDR) to the recto-vaginal septum. According to International Commission Radiation Unit report 38, the dose was prescribed according to disease volume, without a fixed minimum dose at point A [28]. In some cases extended field radiotherapy was used to treat paraaortic lymph nodes involved in the neoplastic process.

External adjuvant radiotherapy (50 Gy) was given four to six weeks after surgical treatment to the patients who showed parametrial neoplastic involvement or lymph node positivity at the final histological examination. Postoperative LDR brachytherapy (30 Gy) was also given to patients with positive surgical resection margins.

Table 1. — *Baseline data of the 288 patients (%).*

	NACT ARM n = 159 (55.2)	CONV arm n = 129 (44.8)	Chi-square	*p*
Patient age			.09	.95 (ns)
< 35 yrs	42 (26.4)	36 (27.9)		
35-50 yrs	36 (22.6)	28 (21.7)		
> 50 yrs	81 (50.9)	65 (50.4)		
FIGO stage			.07	.96 (ns)
Ib-IIa	105 (66.0)	84 (65.1)		
IIb	24 (15.1)	21 (16.3)		
IIIa-IIIb	30 (18.9)	24 (18.6)		
Tumor size	.61	.43 (ns)		
< 5 cm	96 (60.4)	72 (55.8)		
> 4 cm	63 (39.6)	57 (44.2)		
Lymph nodes (radiol. status)			.49	.48 (ns)
Negative	115 (72.3)	98 (76.0)		
Positive	44 (27.7)	31 (24.0)		

* median age 48.5 years (range 32-65 yrs).

Follow-up

After completing the treatment, patients were evaluated every four months for the first two years, every six months during the fourth and fifth years and, subsequently, one time a year (up to 84 months). Pelvic examination, cervical or vaginal Pap smear, colposcopy, histological examination of any bioptic samples, urography and radiological examinations such as CT and/or MRI were performed to assess disease status and degree of treatment-related toxic effects.

Randomization and statistical methods

Randomization was done by means of a computer generated algorithm that divided the patients in two homogeneous arms according to the parameters considered: age, tumor size, FIGO stage and radiological state of the lymph nodes (Table 1). In order to assign more patients to the presumably favorable treatment arm we decided to allocate 55% of the patients to the NACT arm and 45% to the CO arm.

The chi-square test was used to make a statistical evaluation of the frequencies by nominal variables (patient age, tumor volume, FIGO stage, state of lymph nodes, chemosensitivity of the neoplasia); a value of $p < 0.05$ was considered significant (confidence interval, CI 95%). The Cox method was used for evaluating the prognostic factors independently with greater weight on recurrence of the disease [29]. Local relapses and distant metastases were defined as the recurrence of the disease after a disease-free period between the surgical operation and the last follow-up (limited to 84 months) at which the diagnosis of recurrence was made. Survival was calculated as the period between the initial diagnosis of neoplasia and the patient's last follow-up (limited to 84 months).

Table 2. — *Responsiveness of the primary tumor to neoadjuvant chemotherapy (NACT arm).*

	Total	Complete response		Partial response		No response*		Chi-square test	
	pts 159	pts 36	% (22.6)	pts 90	% (56.6)	pts 33	% (20.8)	value (df)	*p*
Patient age								*3.08*	*ns*
< 35 yrs	42	9	(21.4)	27	(64.3)	6	(14.3)		
35-50 yrs	36	9	(25.0)	21	(58.3)	6	(16.7)		
> 50 yrs	81	18	(22.2)	42	(51.9)	21	(25.9)		
FIGO stage								*2.41*	*ns*
Ib-IIa	105	26	(24.8)	58	(55.2)	21	(20.0)		
IIb	24	6	(25.0)	12	(50.0)	6	(25.0)		
IIIa-IIIb	30	4	(13.3)	20	(66.7)	6	(20.0)		
Tumor size								*20.03*	*001*
< 5 cm	96	27	(28.1)	61	(63.6)	8	(8,3)		
> 5 cm	63	9	(14.3)	29	(46,0)	25	(39,7)		
Lymph nodes (radiol. status)								*9.01*	*.01*
negative	115	28	(24.3)	70	(60.9)	17	(14.8)		
positive	44	8	(18.2)	20	(44.5)	16	(36.4)		

Patients: pts; *stable-progressive disease.

However, the incidence of complications observed after surgical or radiotherapy treatment and of the toxicity found after chemotherapy is not reported here.

Furthermore, the results are compared in terms of overall survival and recurrence of disease between patients that received adjuvant radiotherapy treatment and the group of patients that did not have adjuvant therapies. The SPSS 8.0 statistical software package was used for all analyses.

Results

Response to chemotherapy

Chemotherapy was delayed in 19 cases (12%) for moderate to severe transient, mostly hematologic toxicity, and dose-reduced in six cases (3.8%).

The data related to the response of the primary tumor of the 159 patients with locally advanced cervical carcinoma and assigned to the neoadjuvant chemotherapy arm are summarized in Table 2. The patient characteristics considered for the analysis were: patient age, clinical staging, size of the tumor and lymph node status (preoperative radiological evaluation). A complete response was obtained only in 36 patients (22.6%), a partial response in 90 patients (56.6%) and no response (stable-progressive disease) in 33 patients (20.8%).

No statistically significant differences were observed in responsiveness to chemotherapy in relation to age (< 35 yrs, 35-50 yrs, > 50 yrs) (chi-square = 3.08; $p = 0.54$) and disease Stage (Ib-IIa, IIb, IIIa-IIIb) (chi-square = 2.41; $p = 0.66$).

In patients with Stage Ib-IIa cervical carcinoma the complete responsiveness to chemotherapy was 72.2%, while in patients with carcinoma in Stage IIb and IIIa-IIIb a complete response of 16.7% and 11.1%, respectively, was found.

The tumor size (≥ 5, < 5 cm) was considered relevant to the responsiveness to chemotherapy (chi-square = 20.03; $p = 0.001$). In patients assigned to NACT there were 27 (28.1%) complete response for tumor size < 5 cm and nine (14.3%) partial response for tumor size ≥ 5 cm (14.3.0%).

Finally, response to chemotherapy on the primary tumor in the presence of radiologically ascertained (preoperative) lymph node positivity was evaluated; the difference found between the two groups was statistically significant (chi-square = 9.01; $p = 0.01$). In patients with lymph node positivity on radiological examinations, there was complete response in 18.2% (n = 5), partial in 44.5.2% (n = 20) and no response in 36.4% (n = 16); however, in patients with clinically negative lymph nodes the complete response was 24.3% (n = 28), the partial 60.9% (n = 70) and no response 14.8% (n = 17).

No surgical treatment was performed on six patients classified as Stage III non responsive to chemotherapy of the NACT arm and 24 patients of the CONV arm, at the same stage, and they were therefore excluded from the statistical evaluation.

Histological results

In the 258 responsive patients (Ib-IIb: 234 and IIIa-IIIb: 24), radical hysterectomy with systematic pelvic/aortic lymphadenectomy was performed with a median number of nodes removed of 44 (range 32-56): 27 pelvic (range 21-33) and 17 of the aortic area (range 11-23). Concerning tumor grading: 81 cases were well differentiated, 49 cases moderately differentiated and 128 cases poorly differentiated.

Pathologic examination of the surgical specimens revealed positive surgical margins in 28 (10.8%), parametrial involvement in 78 (30.2%), and lymph node positivity in 66 patients (25.6%).

Adjuvant radiotherapy

After surgical treatment, 84 patients who had at least one of the following risk factors were treated with additional postoperative radiation therapy: positive pelvic/aortic lymph nodes (n = 6), parametrial involvement (n = 4), parametrial involvement and nodes positivity (n = 45), parametrial involvement and/or positive margins (n = 14), parametrial neoplastic involvement, positive margins and lymph node positivity (n = 15).

Table 3. — *Main prognostic factors that influenced the recurrence of the disease* in the 258 patients on whom surgery was performed.*

Prognostic factors	NACT arm					CONV arm				
	Total	Disease recurrence		Chi. square		Total	Disease recurrence		Cox method	
	pts 153	pts 49	% (32.3)		*p*	pts 105	pts 39	% (37.1)		*p*
CLINICAL										
Patient age										
< 35 yrs	42	15	(34.9)			36	15	(4176)		
35-50 yrs	30	10	(33.3)	*.50*		24	5	(20.8)	*3.5*	*.17 (ns)*
> 50 yrs	81	24	(29.6)	*.77 (ns)*		45	19	(42.9)		
FIGO stage										
Ib-IIa	105	25	(23.8)			84	30	(35.7)		
IIb	24	10	(41.7)	*11.9*	*.003*	21	9	(42.9)	*.3*	*.54 (ns)*
IIIa-IIIb**	24	14	(58.3)			/	/			
Tumor size										
< 5 cm	90	20	(22.2)	*9.6*	*.002*	72	17	(23.6)	*17.9*	*.000*
> 5 cm	63	29	(46.0)			33	22	(66.7)		
HISTOLOGICAL										
Tumor grade										
G1	48	10	(20.1)			33	9	(27.3)		
G2	32	9	(28.1)	*5.7*	*.05*	17	6	(35.3)	*2.4*	*.30 (ns)*
G3	73	30	(41.1)			55	24	(43.6)		
Parametrial involvement										
absent	109	27	(24.8)	*9.1*	*.002*	71	18	(25.5)	*13.0*	*.000*
present***	44	22	(50.0)			34	21	(61.8)		
Lymph node status										
negative	115	25	(21.7)	*22.5*	*.000*	77	18	(23.4)	*23.4*	*.000*
positive***	38	24	(63.1)			28	21	(75.0)		
Surgical margins										
free	137	42	(30.7)	*1.1*	*.28 (ns)*	93	33	(35.5)	*.9*	*.32 (ns)*
involvement***	16	7	(43.7)			12	6	(50.0)		
CHEMOTHERAPY										
complete	36	6	(16.7)							
partial	90	28	(31.1)	*10.8*		/	/	/	/	
absent**	27	15	(55.5)	*.005*						

*distant metastasis and local recurrences; **twenty-four patients (NACT arm) in Stage IIIa-IIIb, found sensitive to neoadjuvant chemotherapy, were able to undergo surgical treatment. Six patients in the same stage not responsive to chemotherapy treatment (NACT arm) and 24 patients in the control group (CONV arm) did not undergo surgery and were excluded from the statistical evaluation of recurrences; ***adjuvant radiotherapy treatment was given 4-6 weeks after surgical treatment to 84 patients who showed, at the final histological examination: parametrial neoplastic infiltration and/or lymph node positivity and/or parametrial neoplastic infiltration.

Recurrences

Table 3 shows the main prognostic factors that influenced recurrence of the disease in 153 patients given neoadjuvant chemotherapy and radical surgery (NACT arm) and in 105 patients treated with conventional surgery or exclusively radiotherapy (CONV arm).

No surgical treatment was performed on six patients classified as Stage III who were non responsive to the chemotherapy of the NACT arm and 24 patients of the CONV arm, in the same stage, and they were therefore excluded from this statistical evaluation.

The local recurrence of the disease and the incidence of distant metastasis were evaluated in relation to clinical prognostic factors (patient age, clinical staging, cervical tumor diameter), histological prognostic factors (grading, parametrial infiltration, positive surgical resection margins lymph node positivity) and responsiveness to chemotherapy.

Recurrence of disease was documented in 49 patients of the NACT arm (n = 153) and in 39 patients of the CONV arm (n = 105). Disease-related deaths occurred in 47 patients of the NACT arm (29.6%) and 44 in the CONV arm (34.1%).

No statistically significant differences between the two arms were observed in relation to the age of the patients with regard to disease recurrences, while a significant difference in relation to the stage was noted in the NACT arm group (chi-square = 11.91; $p = 0.003$).

Patients in the NACT arm group showed a recurrence rate of 23.8% FIGO Stage Ib-IIa, 41.7% and 58.3% Stage IIb and III, respectively.

Statistically significant differences were observed in terms of recurrence of disease related to the size of the primary tumor. In patients with a tumor < 5 cm, recurrence of the disease was 22.2%, and in patients with larger tumor sizes ≥ 5 cm, 46.0% contributed to an increase in local and distance recurrences: in the NACT arm (chi-square = 9.65; $p = 0.002$) and in the CONV arm (chi-square = 17.96; $p = 0.001$). In the NACT arm group, the odds ratio (OR) was 2.985 (CI 95% = 1.480-6.022) indicating that patients with tumor size ≥ 5 cm are three times more likely to have recurrences, while in the CONV arm

group the result is higher with an OR = 6.471 (CI 95% = 2.617-16.000).

Statistically significant differences in the recurrence rate were observed in both study groups, for patients with histologically negative prognostic factors as: parametrial infiltration (NACT arm: chi-square = 9.16; $p = 0.002$; OR = 3.037; CI 95% = 1.458-6.326), (CONV arm: chi-square = 13.05; $p = 0.001$; OR = 4.756; CI 95% = 1.984-11.402) and lymph node status (NACT arm: chi-square = 22.50; $p = 0.001$; OR = 6.171; CI 95% = 2.789-13.656), (CONV arm: chi-square = 23.43; $p = 0.001$; OR = 9.833; CI 95% = 3.599-26.866); only in the NACT arm group was a low significant difference (chi-square = 5.74; $p = 0.05$) found related to grading.

Responsiveness to chemotherapy can also influence recurrence of the disease (chi-square = 10.80; $p = 0.005$). Recurrence of the disease was observed in 16.7% of the patients who had shown a complete response to neoadjuvant chemotherapy, in 31.1% of the patients with partial response and in 55.5% of the patients not responsive (stable-progressive disease).

Overall and disease-free survival

Overall and disease-free survival, subdivided for stage and total, are summarized in Tables 4 and 5.

Table 4. — *Overall survival and deaths for stage in NACT and CONV arms (%).*

	NACT arm	CONV arm	Chi-square	*p*
Ib-IIa			.71	.39 (ns)
Overall survival	83 (79.0)	62 (73.8)		
Deaths	22 (21.0)	22 (26.2)		
IIb			.09	.76 (ns)
Overall survival	17 (70.8)	14 (66.7)		
Deaths	7 (29.2)	7 (33.3)		
IIIa-IIIb			.14	.70 (ns)
Overall survival	12 (40.0)	9 (37.5)		
Deaths	18 (60.0)	15 (62.5)		
Total overall survivals and deaths in NACT and CONV arms (%).				
	NACT arm	CONV arm	Chi-square	*p*
Status			1.84	.17 (ns)
Overall survival	112 (70.4)	85 (65.9)		
Deaths	47 (29.6)	44 (34.1)		

Table 5. — *Disease-free survival and recurrences for stage in NACT and CONV groups (%).*

	NACT arm	CONV arm	Chi-square	*p*
Ib-IIa			3.20	.07 (ns)
Disease-free	80 (76.2)	54 (64.3)		
Recurrence	25 (23.8)	30 (35.7)		
IIb			.007	.93 (ns)
Disease free	14 (58.3)	12 (57.1)		
Recurrence	10 (41.7)	9 (42.9)		
IIIa-IIIb				
Disease-free	10 (33,3)	3 (25.0)		
Recurrence	20 (66.7)	6(75.0)		
Total disease-free survivals and recurrences in NACT and CONV groups (%)				
	NACT arm	CONV arm	Chi-square	*p*
Disease-free	104 (65.4)	69 (53.5)	.72	.39 (ns)
Recurrence	55 (34.6)	60 (46.5)		

Of the patients classified as Stage Ib-IIa of the NACT arm (n = 105) and of the CONV arm (n = 84), even though no significant difference was noted, an increase of about 5% in overall 7-year survival was observed in patients classified as Stage Ib-IIa of the NACT arm (79.0%) compared to patients of the CONV arm classified as the same stages (73.8%). On the other hand, a comparison of the disease-free survival in relation to the same groups (Ib-IIa) documents an increase, although not statistically significant in (p: .07) in disease-free survival in the chemotherapy group (76.2%) compared to the control group (64.3%).

The same tables show the results of the follow-up after 84 months and the related overall and disease-free survival of the 45 patients classified as IIb (n = 24) NACT arm and (n = 21) CONV arm. No statistically significant differences between the two groups were found (p = ns). The overall survival was 70.8% in the NACT arm and 66.7% in the CONV arm (chi-square: 0.9; $p = 0.76$) and disease-free 58.3% vs 57.1% (chi-square: 0.07; $p = 0.93$).

In the group of 30 patients classified as Stage III and given neoadjuvant chemotherapy, 24 were found to be responsive to polychemotherapy, which enabled the surgical approach, and six were assigned to radiotherapy. In this group, overall survival was 40.0% (n = 12). Twenty-four patients of the control group (CONV arm) were assigned to radiotherapy: in this group the overall survival was 37.5% (n = 9); there was no statistical difference between the two groups (chi-square: 0.14 and $p = 0.70$).

A comparison between overall and disease-free survival in the NACT and CONV arms is summarized in the same tables. The overall survival in the NACT arm was 70.4% (n = 112) vs 65.9% (n = 85) in the CONV arm (chi-square: 1.86; $p = 0.17$). Disease-free in NACT was 65.4% (n = 104) vs 53.5% (n = 69) in CONV (chi-square: 4.22; $p = 0.04$). Increase in terms of overall and disease-free survival in the NACT arm is mainly linked to 36 patients in whom a complete response to chemotherapy was obtained.

The overall and disease-free survival curves with the Kaplan Meier method, and the determination of degree of significance with the log-rank test are now under evaluation.

Discussion

Several studies have shown the sensitivity to chemotherapy of squamous cell cervical carcinoma [30]. The main purpose of our study was to confirm [31] whether, in diagnosed cases of cervical carcinoma, preoperative chemotherapy could improve the overall survival and disease-free period, and what are the main prognostic factors that influence recurrences.

Concerning response to neoadjuvant chemotherapy, in our clinical experience, a complete response of tumor to chemotherapy was noted in 25% of patients classified as Stages Ib-IIb and in 28% of tumors < 5 cm. The partial and complete response to chemotherapy observed in our study is comparable to that reported by other authors. Chen *et al*. [14] in a study on 142 women with bulky cervical carcino-

ma (Ib2-IIb) had an overall clinical response of 69.4%. Our study registered in 63 cases with tumor size ≥ 5 cm, a total response in 14.3%, a partial in 46.0% and no response in 39.7% cases (chi-square 20.03; $p < 0.001$). If we see the responsiveness of 159 patients who underwent neoadjuvant chemotherapy, we find a total response in 22.6%, a partial response in 56.6% and no response in 20.8% cases. Neoadjuvant therapy enabled a significant increase in the operability of patients even in locally advanced stages [32, 33]. In our study the operable group was increased by 24 chemosensitive cases, which constituted 80% of the patients belonging to Stages IIIa-IIIb. This permitted an increase in survival compared to the group of patients classified as the same stage but not responsive to chemotherapy or to the patients of the control group.

Concerning the recurrences, several authors observed that lymph node positivity is the most important prognostic factor for risk of recurrence [34]. In our study, the presence of lymph node metastasis caused an increase in recurrence, which ranged between 63% ($p < 0.001$) and 75% ($p < 0.0001$) in the NACT and CONV arms, respectively. Recurrence rate from three trials [21-23] could improve an OR favorable to neoadjuvant chemotherapy (OR: 0.76; $p = 0.21$) but the results are not significant. Pathologic findings, in Chen *et al's* study [14] showed that pelvic lymph node metastasis and parametrial infiltration rates were significantly lower in the NACT group than in the primary surgery group ($p = 0.025$; $p = 0.038$). We found no significant difference between the two groups in relapses for involvement of surgical margins, respectively 43.7% and 50%. Relapses were significantly lower in parametrial involvement, respectively, 50% and 61.8% ($p = 0.002$). Chen *et al*. [14] found that NACT responders had a higher tumor-free survival and lower recurrence rate that non-NACT responders ($p = 0.000$; $p = 0.013$). With regard to recurrences Sardi *et al*. [21] observed a significant decrease in pelvic failure ($p < 0.001$). Our study confirms the same results ($p < 0.002$). Eddy and colleagues [23] reached opposite conclusions concerning bulk tumor size with similar recurrence rates (relative risk 0.998) and death rates (RR 1.008) when compared to the NACT group vs surgery alone. We have to note that as far as surgical approach to cervical carcinoma is concerned, it is directly linked to the concept of resectability and radicality, and is justified since this tumor remains localized in the pelvis for a fairly long time [30].

Concerning survival, several authors [35] have reported in randomized studies an increase of the overall survival in patients in Stage IB treated with neoadjuvant chemotherapy, documenting a significant reduction in the aggressivity of the neoplasia on involvement of the parametria and lymph node metastases. When we analyze our results, related to the patients classified Ib-IIa, we find an increase of about 5% in overall and 12% in disease-free 7-year survival, although not statistically significant in the group of patients given neoadjuvant chemotherapy compared to the control group; it was mainly due to the 26 patients completely responsive to the chemotherapy regimen (22.6%) who contributed to this improvement in the survival rate. With regard to bulky tumors (> 4 cm), Sardi *et al*. [21] found statistical significance in overall and disease-free survival of the neoadjuvant plus surgery group vs the control group. This was due, however, in our study, to increased operability of bulky responsive tumors after neoadjuvant chemotherapy ($p < 0.01$).

Data on progression-free survival are also available from three trials [14, 23, 36] with significant benefits from neoadjuvant chemotherapy (hazard ratio 0.76, $p = 0.01$). Disease-free survival in our study was 65.4% in the NACT group vs 53.5% in the CONV group (chi square: 4.22; $p = 0.04$).

The main result which documents total remission of the disease is represented by total regression of the primary focus. Moreover, evaluation of the size of the primary tumor after neoadjuvant treatment allowed us to hypothesize a subsequent treatment strategy: patients showing an excellent response to neoadjuvant chemotherapy could be treated after surgery with successive cycles of chemotherapy; on the other hand, a limited response should suggest withdrawal of the postsurgical chemotherapy protocol and redefining the treatment strategy. For these reasons we think that the combination of neoadjuvant chemotherapy plus surgery and adjuvant radiotherapy (or, if possible, adjuvant chemotherapy) is feasible and does not constitute "overtreatment" for most patients with cervical carcinoma at high risk of recurrence.

It is reasonable to think that the evolution of chemotherapeutic drugs could cause changes in future protocols to the benefit of increased survival results.

Conclusions

Despite the conclusions of Eddy *et al*. [23] who advise against adding NACT to radical surgery in Stage Ib2 cervical cancer cases, the results of several studies suggested that neoadjuvant chemotherapy prior to radical surgery is acceptable in locally advanced cervical cancer. This may reduce the bulky tumor, allowing surgery for patients otherwise inoperable and in which the concept of radicality could not be satisfied, thus improving the prognosis in patients with locally advanced cervical cancer. The prognosis for patients in the control group who could not undergo resection was significantly worse than for those in whom surgery could be performed. From this clinical experiment it can be concluded that cases of cervical carcinoma, with an almost complete responsiveness to the neoadjuvant chemotherapy treatment, benefits both in terms of overall survival and in terms of disease-free survival. The same group of patients could be treated after surgery with cycles of chemotherapy, avoiding adjuvant radiotherapy treatments which are subject to a rather high incidence of complications.

It is to be hoped that the chemotherapeutic agents already in use for so many years and others in the experimental phase can change the present therapeutic approach and, what is more, assign the greatest number of patients to treatment in order to obtain improved disease-free survival in a group of poor prognosis patients.

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