The role of neoadjuvant chemotherapy for squamous cell cervical cancer (Ib-IIIb): a long-term randomized trial

C. Napolitano[1], *M.D.*; **F. Imperato**[2], *M.D.*; **B. Mossa**[2], *M.D.*; **M. L. Framarino**[2], *M.D.*; **R. Marziani**[1], *M.D.*; **L. Marzetti**[2], *M.D.*

[1]*Division of Obstetrics and Gynecology, Sant'Andrea Hospital, II School of Medicine;*
[2]*Department of Gynecological Sciences, Perinatology and Child Health, I School of Medicine;*
University of Rome "La Sapienza" (Italy)

Summary

Objective: to verify whether a regimen of preventive chemotherapy in the treatment of cervical carcinoma allows surgical treatment in a larger number of patients and whether cases treated with this combined neoadjuvant polychemotherapy/surgery regimen improves overall and disease-free survival rates. *Design*: prospective randomized clinical study. *Setting*: Department of Gynaecology and Obstetrics, University of Rome "La Sapienza". *Methods*: 192 patients suffering from squamous cell carcinoma of the uterine cervix in Stages Ib-IIIb were randomized to one of the following treatments: three courses of neoadjuvant chemotherapy with cisplatin, vincristine, bleomycin (NACT arm; n=106); conventional surgery or radiotherapy alone (CO arm; n = 86). One hundred and fifty-six patients in Stage Ib-IIb (n = 86, NACT arm and n = 70, CO arm) and 16 patients in Stage III (NACT arm) who proved to be sensitive to the neoadjuvant chemotherapy, underwent radical hysterectomy. Four Stage III patients not sensitive to chemotherapy and 16 patients, Stage III, of the CO arm underwent radiotherapy. *Results*: the 5-year overall survival rates for the NACT and CO arm, respectively, were 78.6% and 73.2% in Stages Ib-IIa (p = NS), 68.7% and 64.3% in Stage IIb (p = NS). A 5-year disease-free survival rate for the NACT arm and CO arm, respectively, of 77.1% and 64.3% in Stages Ib-IIa ($p < .05$), 56.2% and 57.1% in Stage IIb (p = NS) was found. *Conclusions*: the responsiveness of cervical cancer to neoadjuvant chemotherapy allows surgical treatment in a larger number of patients and results in longer overall and disease-free survival.

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

Introduction

Although in the early stages carcinoma of the uterine cervix has a high possibility of treatment aimed at a permanent cure, the percentage of relapses is high in the presence of certain unfavorable prognostic factors, such as lymph node involvement, tumor-volume, parametrial infiltration, high tumor-grading and invasion of lymph-vascular spaces [1-3].

Chemotherapy, which in the past was considered palliative and/or as a supplement to radiotherapy, was proposed during the eighties as a neoadjuvant regimen to increase the surgical resectability of tumors judged unsuitable for surgery [4, 5]. Neoadjuvant chemotherapy has an undeniable biologic rationale because it represents an in vivo test of chemosensitivity that can influence subsequent therapeutic strategies [6].

Whether the introduction of preoperative chemotherapy effectively improves the overall and/or disease-free survival is controversial. In spite of the many therapeutic protocols for cervical carcinoma proposed during the past 50 years, survival has remained almost unchanged [7].

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Materials and methods

Design

We conducted a prospective, randomized clinical study in 203 consecutive patients with squamous cell carcinoma of the uterine cervix histologically diagnosed in Stages Ib-IIIb. The recruitment started in January 1986 and ended in December 1995 at the Institute of Gynecology and Obstetrics, University of Rome "La Sapienza". Inclusion criteria were age less than 70, absence of severe systemic pathologies or other neoplastic pathologies, absence of neuropathies, leucopoenia (< 3000 mm^3), thrombocytopenia (< 100,000 mm^3), alterations of serum creatinine (> 1.5 mg/dl) or bilirubinemia (> 1.2 mg/dl). One hundred and ninety-two patients were enrolled in this study, with an average age of 49.1 years (range 32-68 yrs).

Patients were clinically staged according to the International Federation of Gynecology and Obstetrics (FIGO; 1985) [8]: 126 patients were classified as Stage Ib-IIa, 30 as Stage IIb and 36 as Stage IIIa-IIIb. To improve clinical staging, in addition to a clinical examination, a bioptic examination, colposcopic examination, cystoscopy and proctoscopy, and other instrumental investigations considered "optional" by FIGO because they cannot alter the neoplasia staging were performed in all patients.

Determination of the tumor size was obtained by an ultrasound of the pelvis and/or nuclear magnetic resonance: 112 patients showed tumor size of < 5 cm (58.3%), while a tumor size of > 5 cm was documented in 80 patients (41.7%).

In addition, the pelvic lymph node and aortic area involvement was radiologically evaluated (lymphangiography, CT) before any therapy; neoplastic involvement of the pelvic and/or paraaortic lymph nodes was diagnosed in 52 out of 192 patients.

Subsequently patients were randomized into two groups (Figure 1): 106 patients were given neoadjuvant chemotherapy (NACT arm) and 86 were the control group treated with conventional surgery or radiotherapy alone (CO arm). Informed consent was obtained from each patient before randomization. The study was approved by the Ethical Committee of this University.

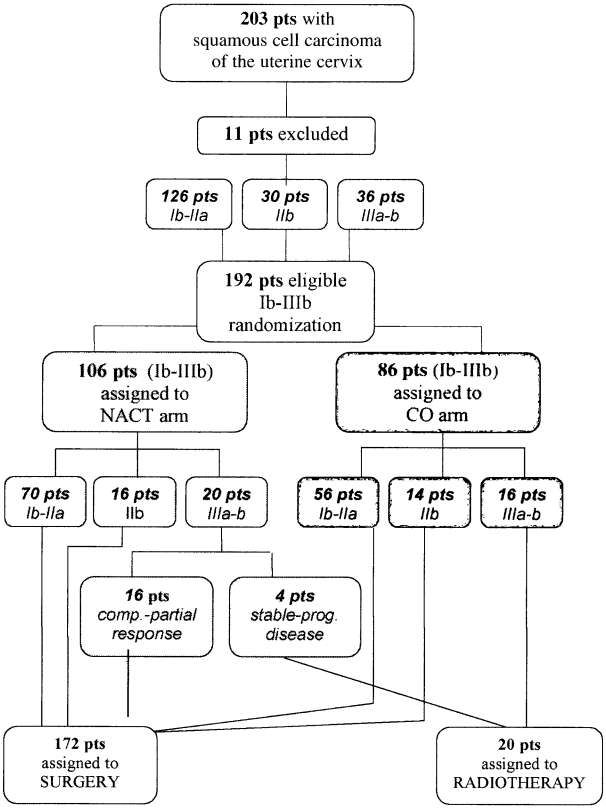


Figure 1. — Trial profile (n = 192).

Neoadjuvant chemotherapy and evaluation of tumor response

In the group that received neoadjuvant chemotherapy a polychemotherapy regimen with cisplatin, vincristine, bleomycin (PVB) was used. The full neoadjuvant chemotherapy consisted of three cycles 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 administration, hematochemical and instrumental tests were done, such as complete hemochrome, plasmatic indexes of renal and liver function, study of respiratory function, and radiological pulmonary control. The toxicity of the chemotherapeutic drugs was evaluated according to the World Health Organization guidelines (WHO, 1979) [9]. The cycles were delayed one week if leukocytes were between 2,000 and 3,000 mm^3 and platelets were between 50,000 and 100,000 mm^3. If the symptoms persisted for more than seven days vincristine was reduced to 50% of the normal dose, while the doses of bleomycin and cisplatin were not changed.

Clinical examination, colposcopy and pelvic echography were used to evaluate the responsiveness of the primary tumor to chemotherapy and the therapeutic response was classified according to the WHO criteria [9].

Surgical procedure

One hundred and fifty-six patients in Stage Ib, IIa and IIb (n-86 NACT arm and n-70 CO arm) underwent type III-IV radical hysterectomy according to Piver [10] with systematic lymph-node dissection of the lumbar-aortic area as well as pelvic lymphadenectomy (modified radical hysterectomy according to Wertheim-Valle) [11-12]. Furthermore, the group of patients undergoing surgical treatment was increased by 16 patients (NACT arm) in Stage IIIa-IIIb for whom it was possible to satisfy the concept of radicality because they had proved sensitive to the neoadjuvant chemotherapy. The surgical operation was performed on the recruited patients, within four weeks of completion of the neoadjuvant chemotherapy.

A macroscopic evaluation was systematically made on the surgical specimens of the residual tumor as well as a histological study of the uterine cervix, parameters, paracolpia and of all the lymph-node stations 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 = 16) or those treated with neoadjuvant chemotherapy but with tumors not responsive to the chemotherapeutic drugs (n = 4). In these cases patients were started on radiotherapy and were initially treated with external-beam radiotherapy on the whole pelvis (50 Gy) for five or 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 tumor volume without a fixed minimum dose at point A [13]. 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 infiltration or lymph node positivity at the final histological examination. Patients with neoplastic affections of the edges of the surgical resection were also given LDR brachytherapy (30 Gy).

Follow-up

After completing the treatment, patients were followed-up every six months for the first year and then every 12 months (up to 60 months); this included an objective examination, cervical or vaginal Pap test, histological examination of any bioptic samples, urography and radiological examinations such as CT and/or MR.

Randomization and statistical methods

Randomization was done by means of an 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-

Table 1. — *Baseline data of 192 patients (%).*

	NACT arm		Co arm		Chi-square test	
	pts 106	% (55)	pts 86	% (45)	value (df)	p
Patient age*						
< 35 yrs	28	(26.4)	24	(27.9)		
35-50 yrs	24	(22.6)	19	(22.1)	$.054_2$	NS
> 50 yrs	54	(51.0)	43	(50.0)		
FIGO stage						
Ib-IIa	70	(66.0)	56	(65.1)		
IIb	16	(15.1)	14	(16.3)	$.051_2$	NS
IIIa-IIIb	20	(18.9)	16	(18.6)		
Tumor size						
< 5 cm	64	(60.4)	48	(55.8)	$.407_1$	NS
> 5 cm	42	(39.6)	38	(44.2)		
Lymph nodes (radiol. status)						
negative	77	(72.6)	65	(75.6)	$.213_1$	NS
positive	29	(27.4)	21	(24.4)		

*average age 49.1 years (range 32-68 yrs)

volume, FIGO stage, state of the lymph nodes, chemosensitivity of the neoplasia); a value of $p < .05$ was considered significant (confidence interval 95%). The Cox method was used to evaluate the prognostic factors independently with greater weight on recurrence of the disease [14]. Local relapses and distant metastases were defined as recurrence of the neoplastic disease after a disease-free period between the surgical operation and the last follow-up (limited to 60 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 60 months). The Kaplan and Meier method was used for the curve of survival without signs of disease (of recurrence) and overall survival [15]. The log-rank test was used to compare the curves and determine the degree of significance [16].

However, the incidence of the complications observed after surgical or radiotherapy treatment and of the toxicity found after chemotherapy is not reported here. Furthermore, the results are not compared in terms of overall survival and recurrence of disease between the patients who 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

Due to toxicity, chemotherapy was delayed in 13 cases (12.3%) and dose-reduced in four cases (3.8%). The data related to the response of the primary tumor of the 106 patients suffering from cervical carcinoma and assigned to the neoadjuvant chemotherapy arm are summarized in Table 2. The parameters considered for the analyses were patient age, clinical staging, size of the tumor and lymph node state (preoperative radiological evaluation). A complete response was obtained in only 24 patients (22.6%), a partial response in 60 patients (56.6%) and no response (stable-progressive disease) in 22 patients (20.8%).

No statistically significant differences were observed (p = NS) in responsiveness to chemotherapy in relation to age (< 35 yrs, 35-50 yrs, > 50 yrs) and disease staging (Ib-IIa, IIb, IIIa-IIIb). In patients with Stage Ib-IIa cervical carcinoma the complete responsiveness to chemotherapy was 24.3%, while in patients with carcinoma in Stage IIb and IIIa-IIIb a complete response of 25.0% and 15.0%, respectively, was found.

The tumor size (< 5 cm, > 5 cm) was considered relevant to the responsiveness to chemotherapy ($p < .0001$). Complete responsiveness to chemotherapy for a tumor with dimensions < 5 cm was doubled (28.3%) as compared to neoplasias with an extension > 5 cm (14.3%).

Finally, response to chemotherapy on the primary tumor in the presence of radiologically ascertained (preo-

Table 2. — *Responsiveness of the primary tumor to neoadjuvant chemotherapy (NACT arm) evaluated by clinical examination, colposcopy and pelvic echo (%).*

	Total	Complete response		Partial response		No response*		Chi-square test	
	pts 106	pts 24	% (22.6)	pts 60	% (56.6)	pts 22	% (20.8)	value (df)	p
Patient age*									
< 35 yrs	28	6	(21.4)	18	(34.3)	4	(14.3)		
35-50 yrs	24	6	(25.0)	14	(58.3)	4	(16.7)	2.055_4	NS
> 50 yrs	54	12	(22.2)	28	(51.9)	14	(25.9)		
FIGO stage									
Ib-IIa	70	17	(24.3)	39	(55.7)	14	(20.0)		
IIb	16	4	(25.0)	8	(50.0)	4	(25.0)	4.733_4	NS
IIIa-IIIb	20	3	(15.0)	13	(65.0)	4	(20.0)		
Tumor size									
< 5 cm	64	18	(28.1)	41	(64.1)	5	(7.8)	16.768_2	< .0001
> 5 cm	42	6	(14.3)	19	(45.2)	17	(40.5)		
Lymph nodes (radiol. status)									
negative	77	19	(24.7)	47	(61.0)	11	(14.3)	7.167_2	< .03
positive	29	5	(17.3)	13	(44.8)	11	(37.9)		

*Stable-progressive disease

perative) lymph node positivity was evaluated; the differences found between the two groups for this parameter showed only a trend to significancy ($p < .03$). In patients with lymph node positivity on radiological examination, the responses defined as complete on the tumor were 17.3% (n = 5), partial results were 44.8% (n = 13) and absent responses 37.9% (n = 11); however, in patients with lymph node negativity the complete responses were 24.7% (n = 19), the partial responses were 61.0% (n = 47) and no response 14.3% (n = 11).

Histological results

In the 172 patients who underwent surgery (n = 156, Ib-IIb and n = 16, IIIa-IIIb chemo-sensitive) the average number of lymph nodes removed was 47 (range 31-89): 29 pelvic (range 21-38) and 18 from the lumbo-aortic

Table 3. — *Main prognostic factors that influence the recurrence of the disease* in the 172 patients on whom surgery was performed (%).*

PROGNOSTIC FACTORS	NACT arm				CO arm			
	Total	Disease recurrence		Cox method	Total	Disease recurrence		Cox method
	pts 102	pts 33	% (32.3)	p	pts 70	pts 26	% (37.1)	p
CLINICAL								
Patient's age								
< 35 aa	28	10	(35.7)		24	10	(41.6)	
35-50 aa	20	7	(35.0)	NS	16	3	(18.7)	NS
> 50 aa	54	16	(29.6)		30	13	(43.3)	
FIGO stage								
Ib-IIa	70	17	(24.3)		56	20	(35.7)	
IIb	16	7	(43.7)	< .01	14	6	(42.9)	< .05
IIIa-IIIb**	16	9	(56.2)		/	/		
Tumor size								
< 5 cm	60	13	(21.7)	< .01	48	11	(22.9)	< .001
> 5 cm	42	19	(45.2)		22	15	(68.2)	
HISTOLOGIC								
Grading-tmor								
G1	32	7	(21.9)		22	6	(27.3)	
G2	21	6	(28.6)	< .05	11	4	(36.4)	< .05
G3	49	20	(40.8)		37	16	(43.2)	
Parametrial involvement								
absent	73	18	(24.7)	< .01	47	12	(25.5)	< .01
present***	29	15	(51.7)		23	14	(60.8)	
Lymph node status								
negative	77	17	(22.1)	< .001	51	12	(23.5)	< .0001
positive***	25	16	(64.0)		19	14	(73.7)	
Surgical margins								
free	91	28	(30.8)	< .01	62	22	(35.5)	< .01
involvement***	11	5	(45.4)		8	4	(50.0)	
CHEMO								
complete	24	4	(16.7)					
partial	60	19	(31.7)	< .01	/	/	/	/
absent**	18	10	(55.5)					

*distant metastasis and local recurrences.

** Sixteen patients (NACT arm) in Stage IIIa-IIIb, found sensitive to neoadjuvant chemotherapy, were able to make use of surgical treatment. On the other hand, four patients in the same stage not responsive to chemotherapy treatment (NACT arm) and 16 patients in the control group (CO 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 56 patients who showed at the final histological examination: parametrial neoplastic infiltration (n=3), lymph node positivity (n=4), parametrial neoplastic infiltration and lymph-node positivity (n=30), parametrial neoplastic infiltration and neoplastic affection of the surgical exeresis margins (n=9), parametrial neoplastic infiltration, surgical resection margins compromised by neoplasia and lymph-node positivity (n=10).

region (range 11-23). Concerning tumor-grading: 54 cases were well differentiated, 32 cases moderately differentiated and 86 cases non-differentiated.

In 19 of the 172 patients (11%), a neoplastic affection of the surgical exeresis margin was documented; neoplastic infiltration of the parameters was documented in 52 patients (30.2%). Forty-four patients (25.6%) showed lymph node positivity at the final histological examination.

Adjuvant radiotherapy

After surgery, 56 patients were given radiotherapy: three patients for parametrial neoplastic involvement, four patients for lymph-node positivity, three patients for parametrial neoplastic involvement and lymph-node positivity, nine patients for parametrial neoplastic involvement and neoplastic affection of the surgical exeresis margins, ten patients for parametrial neoplastic involvement, with margins of the surgical resection compromised by neoplasia and lymphnodal positivity.

Recurrences

Table 3 shows the main prognostic factors that influence recurrence of the disease in the 102 patients given neoadjuvant chemotherapy and radical surgical treatment (NACT arm) and in the 70 patients constituting the control group (CO arm). On the other hand, no surgical operation was performed on four patients classified as Stage III not responsive to the chemotherapy of the NACT arm and 16 patients of the CO arm, at 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, extension of the primary tumor), histological prognostic factors (grading, parametrial infiltration, margins of the surgical resection compromised by neoplasia, lymph node positivity) and responsiveness to chemotherapy.

Recurrence of the disease was documented in 33 patients of the NACT arm (n = 102) and in 26 patients of the CO arm (n = 70). Disease-related deaths occurred in 29 patients of the NACT arm and 20 in the CO arm.

No statistically significant variations in relation to the age of the patient (p = NS) were noted in terms of recurrence of the disease, while a significant difference in relation to the stage was noted in the two study groups ($p < .01$ NACT arm, $p < .05$ CO arm). For patients classified as Stage Ib-IIa the recurrence of the disease was 24.3% in the NACT arm and 35.7% in the CO arm; for patients classified as Stage IIb it was 43.75% in the NACT arm and 42.9% in the CO arm and for patients of the NACT arm classified as Stage III the recurrence of the disease was 56.2%. Statistically significant differences were observed in terms of recurrence of the disease in relation to the size of the primary tumor. In patients with a tumor < 5 cm, recurrence of the disease was approximately 20% in both groups; larger tumor sizes, > 5 cm, contributed to an increase in local and distance recurrences in 45.2% of the patients of the NACT arm ($p < .01$) and 68.2% of the patients in the CO arm ($p < .001$).

Statistically significant differences in the recurrence of the disease were noted, in both study groups for the following categories (histological prognostic factors): grading ($p < .05$), parametrial infiltration ($p < .01$) lymph node status ($p < .001$ NACT arm, $< .0001$ CO arm) and surgical exeresis margins ($p < .01$).

Responsiveness to chemotherapy can also influence recurrence of the disease ($p < .01$). Recurrence of the disease was observed in only 16.7% of the patients who had shown a complete response to the chemotherapy treatment, in 31.7% of the patients in whom a partial response was noted and in 55.5% of the patients not responsive to neoadjuvant chemotherapy (stable-progressive disease).

Overall and disease-free survival

The following diagrams (Figures 2 and 3) show the results, in terms of both overall and disease-free survival, of the patients classified as Stage Ib-IIa of the NACT arm

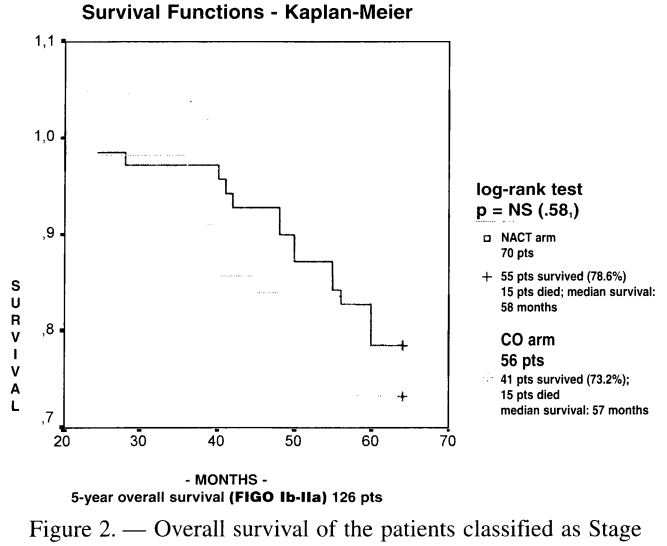


Figure 2. — Overall survival of the patients classified as Stage Ib-IIa.

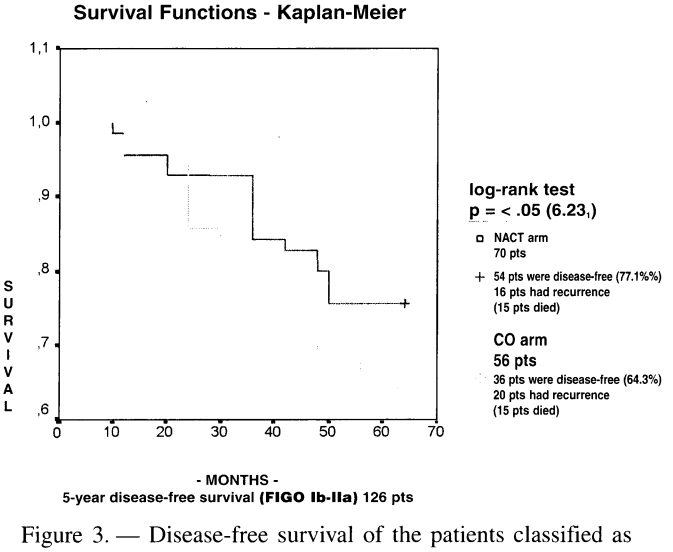


Figure 3. — Disease-free survival of the patients classified as Stage Ib-IIa.

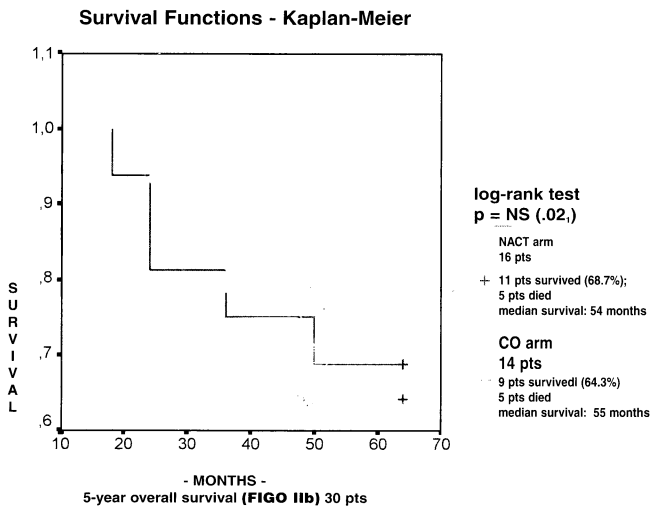


Figure 4. — Overall survival of the patients classified as Stage IIb.

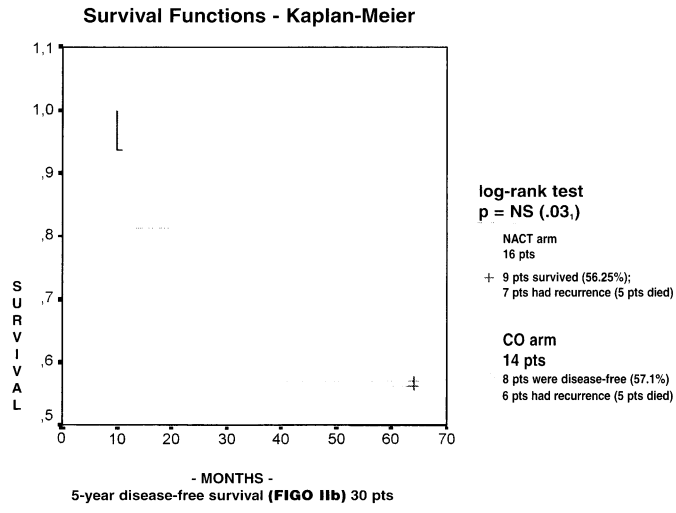
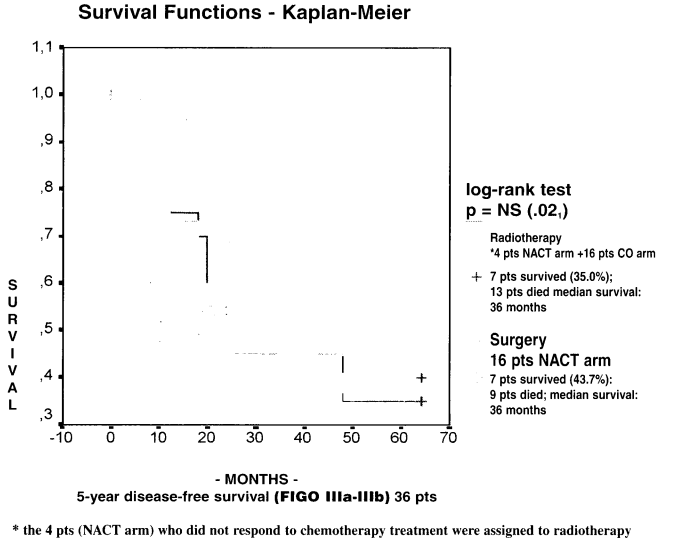


Figure 5. — Disease-free survival of the patients classified as Stage IIb.

(n = 70) and of the CO arm (n = 56). Even though significant differences (p = NS) were not noted for the two study groups, an increase of about 5% in the incidence of overall 5-year survival was observed in the 70 patients classified as Stage Ib-IIa of the NACT arm (78.6%) compared to 56 patients of the CO arm classified as the same stages (73.2%). The increase in terms of overall survival of the NACT arm is mainly linked to the 17 patients in whom a complete response to chemotherapy was obtained (Figure 2). The median survival (limited to 60 months) was 58 months in the NACT arm (95% CI, 56-59 months) and 57 months in the CO arm (95% CI, 55-58 months). On the contrary, a comparison of the curves related to survival without signs of disease in relation to the same groups (Ib-IIa) documents a statistically significant increase ($p < .05$) in disease-free survival in the chemotherapy group (77.1%) compared to the control group (64.3%) (Figure 3).

Figures 4 and 5 show the results of the follow-ups after 6, 12, 24, 36, 48 and 60 months and the related overall survival and survival without signs of disease curves of the 30 patients classified as IIb (n = 16, NACT arm and n = 14, CO arm). No statistically significant differences between the two arms in these patients were found (p = NS). The median survival (limited to 60 months) was 54 months in the NACT arm (95% CI, 47-60 months) and 55 months in the CO arm (95% CI, 48-60 months).

In the group of 20 patients classified as Stage III and given neoadjuvant chemotherapy, 16 patients were found to be responsive to polychemotherapy, which enabled the surgical approach. In this group the overall survival was 43.7% with a median survival of 36 months (95% CI, 25-48 months). The four patients who did not respond to chemotherapy treatment and the 16 patients who constituted the control group in Stage III (n = 4, NACT arm and n = 16, CO arm) were assigned to radiotherapy: in this group the overall survival was 35.0% with a median survival of 36 months (95% CI, 25-46 months). A comparison between the overall survival curves of the patients



* the 4 pts (NACT arm) who did not respond to chemotherapy treatment were assigned to radiotherapy

Figure 6. — Overall survival of the patients classified as Stage IIIa-IIIb.

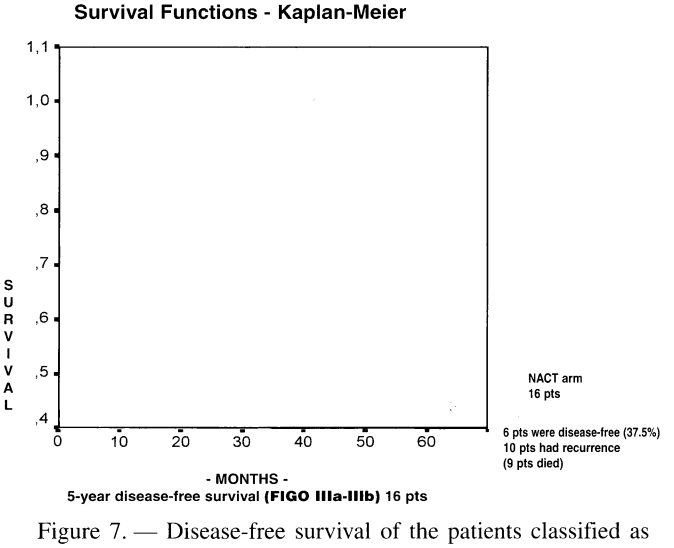


Figure 7. — Disease-free survival of the patients classified as Stage IIIa-IIIb on whom surgery was performed because they were responsive to chemotherapy.

treated with surgery or radiotherapy documents no significant differences (p = NS) (Figure 6). Figure 7 shows the results in terms of disease-free survival (37.5%) obtained in the 16 patients classified as Stage III and on whom surgery was performed because they were responsive to chemotherapy.

Discussion

Several studies have shown the sensitivity to chemotherapy of squamous cell cervical carcinoma [17]. The main purpose of our study was to verify whether, in newly-diagnosed cases of cervical carcinoma, preoperative chemotherapy could improve the overall survival and/or increase the disease-free phase. On the other hand, we did not evaluate whether this therapeutic approach could avoid postsurgical radiotherapy, which, according to several authors, causes greater morbidity and contributes irrelevantly to the overall survival results [18-21].

Bolis G. *et al.* [22] reported, in a randomized study, 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 parameters and on lymph node metastases. In our clinical experience, a complete response of the tumor to chemotherapy drugs was noted in patients classified as Stages Ib-IIb (25%) and for tumors < 5 cm (28%). The partial and complete response to chemotherapy observed in our study is comparable to that reported by other authors (79.2%). The main result, which documents a total remission of the disease, is represented by total regression of the primary focus. Moreover, the 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.

When we analyze our results, related to the patients classified Ib-IIa (n = 126), we find an increase of about 5% in overall 5-year survival, not statistically significant though, in the group of patients given neoadjuvant chemotherapy compared to the control group; it was mainly the 17 patients completely responsive to the chemotherapy regime (24.3%) who contributed to this improvement in the survival index.

On the other hand, neoadjuvant therapy enabled a significant increase in the operability of patients even in advanced stages [23, 24]. In our study the operable group was increased by 16 chemosensitive cases, which constituted 80% of the patients belonging to Stages IIIa-IIIb. This permitted an increase in overall survival compared to the group of patients classified as the same stage but not responsive to chemotherapy or to the patients constituting the control group, probably due to the additional surgical treatment performed on the patients.

The group of patients with lymph node metastasis is interesting; several authors observed that this is the most important prognostic factor for risk of recurrence [25]. Since survival is influenced by distant recurrence, additional treatment appears to be necessary. In our study, the presence of lymph node metastasis caused an increase in recurrence which ranged between 40% ($p < .001$) and 50% (< .0001) in the NACT and CO arms, respectively. Lo Vecchio *et al.* [26] report that in patients with lymph node metastasis, documented by laparotomy, most recurrences occurred in the same place where the compromised lymph nodes were localized and this would suggest giving adjuvant chemotherapy or radiotherapy.

On the contrary, the use of radiotherapy when there is lymph node positivity is controversial. In these cases postsurgical radiotherapy would not improve global survival but would reduce the incidence of pelvic recurrences [27].

Tattersall M. *et al.* [28] studied the survival of patients with lymph node metastasis treated with radiotherapy or with three cycles of chemotherapy (PVB): the different treatment did not cause significant differences between these two groups in terms of overall survival.

A comparative study of three therapeutic strategies: "conventional treatment", "neoadjuvant chemotherapy with adjuvant radiotherapy" and the "sandwich" scheme (neoadjuvant chemotherapy, surgery and adjuvant chemotherapy), seems to indicate chemotherapy with adjuvant radiation therapy on the whole pelvis. In fact, in the group with "sandwich" treatment (neoadjuvant chemotherapy, surgery and adjuvant chemotherapy) a lower incidence of distant lymph-node metastasis was observed but with a higher incidence of recurrence of the disease in the pelvic region, compared to the cases that underwent postsurgical radiotherapy [29].

As far as the surgical approach to cervical carcinoma is concerned, it is directly linked to the concept of resectability and radicality and is justified by the fact that this tumor remains localized in the pelvis for a fairly long time [30]. In carcinoma of the uterine cervix, if the pelvic lymph nodes are negative, the paraaortic lymph nodes are almost always exempt from metastatic replication. In cases of lymph node metastasis to the pelvis, in some patients the lymph nodes might also be affected in the lumbar area; the incidence of neoplastic affection of the paraaortic lymph nodes, reported by Burghardt and Averette [31, 32] is about 8% for Stage Ib2, 14-17% for Stage II and as much as 34% for Stages IIIa-IIIB.

In the treatment of cervical carcinoma, paraaortic and pelvic lymphadenectomy with integral stripping up to the adventitia of the whole areolar tissue, especially if performed during Stages II and III (the latter treated preoperatively with chemotherapy) seems to permit longer survival than exeresis of the pelvic lymphatic network. This procedure allows the removal of a greater number of lymph nodes and the interruption of most of the collectors between the neoplastic focus and the cistern of the cisterna chyli, drainage station of most of the lymph originating in the pelvic organs [33].

For these reasons we propose that the combination "*neoadjuvant chemotherapy + surgery + post-surgical radiation (or possibly adjuvant chemotherapy)*" is feasible and does not constitute "over-treatment" for most of the patients suffering from cervical carcinoma with high risk of recurrence.

Finally, recent studies show that squamous cell carcinoma of the cervix is sensitive to paclitaxol with complete remission of the lesion in 45% of the cases, i.e., double the results obtained with the drugs used by us in this clinical study [34-36]. A comparative study evaluating the efficacy of neoadjuvant chemotherapy, of a protocol with PVB compared to cisplatin-ifofosfamide-paclitaxol, was started at our institute in 1998. It is reasonable to think that the evolution of chemotherapeutic drugs could cause changes in future protocols to the benefit of the increase in the survival results.

Conclusions

From this clinical experiment it can be concluded that newly diagnosed 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.

Furthermore, in the group of patients with chemosensitive tumors it was possible to perform surgery even in tumors initially considered not resectable and in which the concept of radicality could not be satisfied.

Nevertheless, there is still the problem of tumors at advanced stages, not sensitive to chemotherapy and for which surgical treatment is not feasible or is found to be insufficient: in these cases the only therapeutic alternative is radiotherapy.

It is to be hoped that the new chemotherapeutics already in use for some years and others in the experimental phase can change the present therapeutic approach and, what is more, assign the greatest number of patients to privileged treatment in order to obtain an increase in survival and a more satisfying quality of life.

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Address reprint requests to:
C. NAPOLITANO, M.D.
Via Apulia, 9
00183 Rome (Italy)