

Does adjuvant chemotherapy improve the prognosis of cervical carcinoma with lymph-node metastasis? A long-term follow-up

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Summary

Objective: to verify the efficacy of adjuvant therapy in the prevention of neoplastic recurrence in patients at high risk for lymph-node involvement on surgical examination.

Methods: 72 patients, suffering from squamous cell cervical carcinoma Stage IB-IIB (FIGO) who underwent radical hysterectomy with lymph-node involvement confirmed at the final histological examination, were enrolled. All the patients were treated with adjuvant chemotherapy (AC), which included cisplatin, bleomycin and vinblastine, and were followed for a minimum period of six years. The results were compared with those obtained with a historical group of 78 patients, with comparable age, stage and lymph-node involvement, on whom only radical surgery (RS) was performed.

Results: the average total survival rate of the two groups (RS + AC vs RS) at five years was 63.9% and 55.1%, respectively ($\chi^2 = 1.191$; $p = \text{NS}$). The disease-free interval was 55.6% vs 46.2% ($\chi^2 = 1.324$; $p = \text{NS}$). The best results were obtained in cases where the common iliac lymph-nodes were affected, with the highest survival rate of 16.9% in the RS+AC group, out of a total of 25 cases.

Conclusions: adoption of adjuvant chemotherapy in patients at high risk for lymph-node positivity did not produce statistically significant results in terms of overall and disease-free survival; however, a small number of these patients, approximately 9%, could receive benefit from the treatment.

Key words: Cervical cancer; Adjuvant chemotherapy; Lymph-node metastasis.

Introduction

Although the incidence of carcinoma of the cervix has reduced in recent years, this neoplasia is still the third most frequent in woman. There is a high level of curability of lesions in the early phase if the lymph nodes are not affected: in fact, whereas in Stage IB or IIA with negative lymph nodes the disease relapses in only 15% of cases, in the same stages the percentage of recurrences varies between 20 and 75% if there is lymph node involvement [1-5].

However, there are other risk factors, such as size of the tumor, deep invasion of the stroma and involvement of the lymphatic and/or vascular spaces, which worsen the prognosis [6, 7]. However, the most unfavorable prognostic factor remains involvement of the lymph nodes: actuarial five-year survival is, in fact, 91% and 88% for Stage IB or IIA, respectively, versus 68% and 52% in cases of positive lymph nodes [5-8]. Furthermore, the risk of recurrence is related to the number and site of the lymph nodes affected [9-11].

For many years adjuvant therapies have been introduced after radical hysterectomy in an attempt to eradicate

micrometastatic foci in patients at high risk of recurrence due to lymph node positivity [12]. Furthermore, evidence of the efficacy of polychemotherapy in advanced neoplasias [13], as well as the reduction of positive lymph nodes in patients treated with neoadjuvant polychemotherapy [14] and, lastly, the failure of radiotherapy in the control of extra-pelvic recurrences [15, 16] have constituted the rationale for the approach with adjuvant chemotherapy in patients on whom radical surgery is performed and where histology reveals lymph nodes involved in the neoplastic disease. Unfortunately, definitive data are not available so far. A report of the American Gynecologic Oncologists Society concludes that survival after radical surgical treatment is not influenced by adjuvant therapy when the number of positive lymph nodes is greater than three [15]; similar results are reported by other authors [16-19]. Some non-randomized studies suggest benefit from the use of chemotherapy in Stages IB, IIB in the presence of several risk factors, including lymph node metastasis, in 16/28% of the cases [20-22].

Tattersall M. *et al.*, on the other hand [23], in a randomized trial on women after radical hysterectomy and pelvic lymphadenectomy, reported no significant difference in the disease-free interval and overall survival in women receiving adjuvant chemotherapy.

On the basis of these observations, we performed a study aimed at verifying the efficacy of adjuvant chemotherapy in women at risk of recurrence due to histological ascertained lymph node positivity, FIGO Stages Ib, IIa, IIb, started in 1987 and ended in 2001.

The data obtained were compared and statistically evaluated in relation to a similar group of patients on whom only radical surgery was performed.

Materials and methods

The study was carried out on patients operated on for squamous cell carcinoma of the cervix in Stages IB, IIA, IIB with histologically confirmed pelvic and/or lumbo-aortic lymph-node metastasis.

Surgical recruitment opened on 31 January, 1987 and closed on 30 December, 1995 at the *Department of Gynaecology and Obstetrics* University of Rome "La Sapienza". The follow-up was completed and evaluated on 31 December, 2001. The patients were staged according to the system proposed by FIGO in 1985. The study was approved by Ethical Committee of this University.

Admission

The inclusion criteria were: squamous cell carcinoma in Stages IB–IIA–IIB treated with radical surgery; histologically ascertained pelvic and/or para-aortic lymph node metastasis; free margins of tumor; age less than 65 years (average age 48 years); absence of severe systemic diseases; absence of other malignant neoplasias; informed consent of the patient.

Initially 82 patients were taken into consideration, of which ten were excluded from the study: five (6%) because they did not complete the chemotherapy cycles, two because of death due to causes unrelated to the original diseases, three because they were lost to follow-up. The final analysis was therefore based on 72 patients. The average follow-up was ten years (range 6 - 14).

Surgery

All the patients underwent an abdominal radical Piver 3-4 hysterectomy (RS) [24]. Wertheim-Valle integral lymphadenectomy [25] was adopted for dissection of the lymph-nodes. The lymphadenectomy therefore involved removal of all the lymphatic adipose tissue up to the adventitia, along the external and internal iliac vessels, in the obturator groove up to the pelvic floor, along the common iliacs up to the aortic bifurcation, on the promontory of the sacrum and along the para-aortic chain.

An average of 48 lymph nodes were removed from each patient (range 15-65), of which on average: 26 pelvic, 7 common iliac and 15 lumbo-aortic. The number and site of the positive lymph nodes and related frequencies of recurrence and survival were defined.

Chemotherapy

Adjuvant chemotherapy (AC) was started two weeks after the operation according to the PVB scheme: cisplatin 60 mg/m² on day 1, vinblastine 4 mg/m² on days 1 and 2 and bleomycin 15 mg on days 1-8-15 at intervals of three weeks for a maximum of two cycles. The cycles were delayed by one week for leukocytes between 2,000 and 3,000/mm³ and platelet counts lower than 50,000/mm³. Persistence of the situation for more than seven days led to a reduction of vinblastine to 50% of the normal dose while the doses of bleomycin and cisplatin were

not changed. Chemotherapy was suspended if the value of the white corpuscles was less than 2,000 and platelets less than 50,000. The toxicity of the chemotherapy drugs was evaluated according to the WHO guidelines (1979). Five patients (6%) were unable to complete the chemotherapy because of the seriousness of the side-effects.

Control Group

Control was performed on a group of patients who were similar in relation to admission criteria, stage (reclassified according to FIGO 1985) and lymph node affection, on whom only radical surgery therapy (RS) was performed during the period 1961-79. Seventy-eight cases were selected out of 699 treated with integral lymphadenectomy [26, 27]. Operations and follow-up were performed by the same surgical-oncological team.

The overall survival, disease-free survival, recurrences and sites of recurrence were taken into consideration for each group.

The relations between FIGO stage (IB, IIA, IIB), site (pelvic, common iliac, aorto-caval) and number (1-2, greater than 2) of the positive lymph nodes and the related recovery indexes were determined. Lastly, overall survival was evaluated.

Follow-Up

The patients were followed-up according to the scheme shown in Table 1. The average follow-up of the group studied was 120 months (range 72–168 months). Three patients (4.2%) were lost to follow-up, and two (2.7%) died due to causes unrelated to the disease.

The distribution of the prognostic variables does not change whether the patients lost to follow-up are included or excluded ($p = NS$).

Study of the follow-up of the control group was limited to the same period of observation (120 months).

Table 1. — *Post-surgical follow-up of patients with carcinoma of the cervix.*

Years Months	First and second			Third		Fourth and fifth		More than 5
	4	8	12	6	12	6	12	
Clinical examination	+	+	+	+	+	+	+	+
Colposcopy/cytology	+	+	+	+	+	+	+	+
Tumor markers	+	+	+	+	+	+	+	+
Ultrasound / CT			+		+		+	
Laboratory tests	+	+	+	+	+			

Statistical Evaluation

The chi-square test was used for statistical evaluation of the frequencies of the nominal variables or by category: a value of $p < .05$ was regarded as significant.

Survival was calculated as the period between the initial diagnosis of neoplasia with surgical staging and the last follow-up. Recurrences and/or metastases were defined as recurrence of the neoplastic disease after a disease-free period between the surgical operation and the last follow-up. The log-rank test was used to compare curves and degree of significance for survival without signs of disease and overall survival.

Results

The characteristics of the patients are reported in Table 2. The two groups studied were found, in relation to each of the parameters considered (age, staging, number and site of the lymph nodes affected) to be homogeneous and there were no significant differences.

Table 2. — *Clinical-pathological characteristics of the patients included in the study (%)*.

	RS + AC	RS	Significance	
Total patients	72	78	χ^2 test	p
Average age	48	48.9		NS
FIGO stage				
Ib	43 (59.7)	45 (57.7)		
IIa	14 (19.4)	15 (19.2)	.113	NS
IIb	15 (20.9)	18 (23.1)		
Lymph-node invasion				
1-2 (number)	42 (58.3)	45 (57.7)		
≥ 3 (number)	30 (41.7)	33 (42.3)	.057	NS
pelvic	54 (75.0)	56 (71.8)		
common iliac	11 (15.3)	13 (16.7)	.223	NS
paraortic	7 (9.7)	9 (11.5)		

Tolerance to the treatment and complications

Both the surgical treatment (total 150 cases) and the chemotherapy (72 cases) were quite well tolerated. No treatment-related deaths occurred. In particular, there were no severe intraoperative surgical complications. Blood transfusions were given in 7.3% of the cases; postoperative vesical dysfunctions occurred in 20% of the cases and lymphorrhages in 18.4%, without any lymphocysts since systematic drainage of the pelvic cavity was done, with an average of 7.5 days.

Three cases (2%) of urethral fistula occurred which were subsequently repaired: two surgically and one by inserting a double J, and four cases (2.8%) of bladder lesions repaired intraoperatively.

It was not possible to complete the chemotherapy in five patients (6%) who were in any case excluded from the protocol. Toxic effects existed in 20% of the cases of leucopenia, 10% of thrombocytopenia and 25% of serious mucositis. Neurotoxic effects (paresthesia, tremor) were observed in 30% of the cases and regressed after temporary suspension of the treatment.

Result of the treatment

Table 3 shows the overall results of the treatment in the two groups in terms of recurrences and related deaths, disease-free survival and overall survival.

In 72 patients RS + AC no evidence of disease appeared at follow-up in 40 cases (55.6%) while recurrences occurred in 32 cases, equal to 44.4%. The overall survival was 63.9% (46/72) with 26 deaths related to the disease (36.1%).

Overall survival in the control group was 55.1% (43/78; -8.8% compared to the preceding) with 35 deaths

Table 3. — *Results of treatment in patients with high-risk cervical carcinoma (%)*.

	RS + AC	RS	Diff. in %	Significance
Total patients	72	78		χ^2 test p
Overall survival	46 (63.9)	43 (55.1)	8.8	1.191 NS
Mortality	26 (36.1)	35 (44.9)		
Disease-free survival	40 (55.6)	36 (46.2)	9.4	1.324 NS
Metastases	32 (44.4)	42 (53.8)		

(44.9%) ascribable to the original disease. Disease-free survival at five years was 46.2% (36/78; -9.4%).

In relation to death event the relative risk was .80; for RS + AC group add ratio = .57 and for RS group adds ratio = .81. In relation to recurrence event the relative risk was .83; for RS + AC group adds ratio = .80 and for RS group adds ratio = 1.17.

Analysis of recurrences

In Table 4 we have summarized the incidence and site of the recurrences in the two groups.

Table 4. — *Incidence and site of recurrences in the two groups (%)*.

	Total pts. n.	Recurrences		Site of recurrence					
		n.	%	pelvic n.	pelvic %	distant n.	distant %	Related deaths pelvic n.	distant n.
RS + AC treatment	72	32	(44.4)	18	(25.0)	14	(19.4)	14	12
RS treatment	78	42	(53.8)	24	(30.8)	18	(23.0)	19	16

The site of the recurrences shows a higher incidence of recurrence in the control group for both pelvic and distant (30.8% vs 25.0%, 23.0% vs 19.4%).

In the RS + AC group, the 14 patients with extrapelvic recurrence were subsequently given chemotherapy with a non cross-resistant scheme [28] with the precedent: epirubicin alone or ipofosfamide plus MESNA. Instead, the 18 patients with pelvic recurrence had radio/surgical treatment: four patients with pelvic recurrence and two with extrapelvic recurrence obtained remission of disease with the treatment (18.7%).

In the control group (RS), recurrences received radio-surgical treatment only: five patients with pelvic recurrence and two extrapelvic had remission of disease (16.7%). The statistical comparison between deaths in the two groups in relation to metastases was not significant (log rank = .08; p = NS).

Table 5 shows the frequencies of recurrence related to FIGO staging in the two groups. For Stage Ib the frequency was 39.5% vs 46.7%; for Stage IIa the incidence was 50.0% vs 66.7% and lastly 53.3% vs 61.1% for IIb. However the better results obtained in group RS+AC had no statistical significance ($\chi^2 = .339$; p = NS).

Table 5. — Analysis and significance of recurrences by FIGO staging (%).

	Recurrences RS+AC group		Recurrences RS group		Diff. in %	Significance	
	n.	%	n.	%		χ^2 test	p
Stage IB	17/43	(39.5)	21/45	(46.7)	7.2	.339	NS
Stage IIA	7/14	(50.0)	10/15	(66.7)	16.7		
Stage IIB	8/15	(53.3)	11/18	(61.1)	7.8		
Total	32/72		42/78				

In Table 6 we summarize the data related to recurrences by number of positive lymph-nodes.

Table 6. — Analysis and significance of recurrences by number of positive lymph nodes (%).

	Recurrences RS+AC group		Recurrences RS group		Diff. in %	Significance	
	n.	%	n.	%		χ^2 test	p
1-2 lymph nodes	15/42	(35.7)	20/45	(40.5)	4.8	.020	NS
≥ 3 lymph nodes	17/30	(56.7)	22/33	(63.3)	6.6		
Total	32/72		42/78				

By number of positive lymph-nodes less than 3, the percentage of recurrences was 35.7 vs 40.5% in the two groups. For positive lymph-nodes greater than 3 the percentage was, respectively, 56.7 and 63.3% ($\chi^2 = .020$ and $p = NS$).

Lastly, in Table 7 we have summarized the data on recurrences in relation to the site of positive lymph-nodes that were.

The percentages of recurrence in the case of positivity of pelvic lymph nodes are 35.2 vs 42.9% (-7.7%) in the RS+AC group compared to the RS group.

The differences in positivity of the common iliac lymph nodes were considerable 63.6 vs 84.6% (-21%) while the only case of inversion of frequency of recurrences in the ratio between the two groups occurred in the lumbo-aortic lymph nodes (+7.9% in the RS+AC group). However χ^2 was on the whole equal to .199 ($p = NS$).

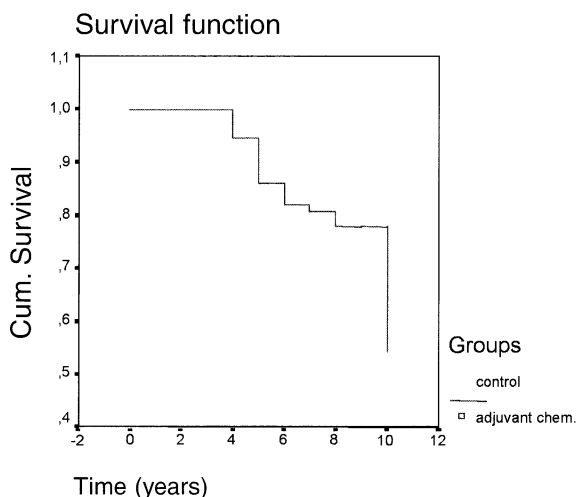


Figure 1. — Overall survival according to treatment.

Table 7. — Analysis and significance of recurrences by site of positive lymph nodes (%).

	Recurrences RS+AC group		Recurrences RS group		Diff. in %	Significance	
	n.	%	n.	%		χ^2 test	p
Pelvic site	19/54	(35.2)	24/56	(42.9)	7.7	.199	NS
Common iliac site	7/11	(63.6)	11/13	(84.6)	21.0		
Paraaortic site	6/7	(85.7)	7/9	(77.8)	7.9		
Total	32/72		42/78				

Analysis of survival by overall statistical comparison

In the following figures we give a comparative analysis of the survival curves of the groups studied using the log-rank test.

Figure 1 shows the overall survivals in the two groups in relation to time. No statistically significant differences appear ($p = NS$), with an average survival of 63.9% in the group that had adjuvant treatment and 55.1% in the control group. On analysis, the estimated risk was 1.213 in the RS+AC group compared to 0.842 in the control group.

Figures 2, 3 and 4 show the comparative survival curves in the two groups in relation to the FIGO staging (Ib, IIA, IIB) without significant differences (log rank = .28, 1.13 and .95, respectively). We must, however, draw attention to the constant better performance obtained in the group receiving adjuvant treatment with a survival of five years for Ib of 69.8 vs 64.4% (+ 5.4%), for IIA of 57.1 vs 46.7% (+ 10.4%) and for IIB of 53.3 vs 38.9% (+14.4%).

From a study of the curves related to the survival/site ratio of positive pelvic, common iliac or lumbo-aortic lymph nodes (Figures 5, 6 and 7), the use of adjuvant chemotherapy in the lumbo-aortic nodes appears paradoxically less useful, with a log rank of 1.05, .84 and .40, respectively ($p = NS$).

The percentage survival differences between the two groups are in order: +8.0%, +17.0% and -10.7%.

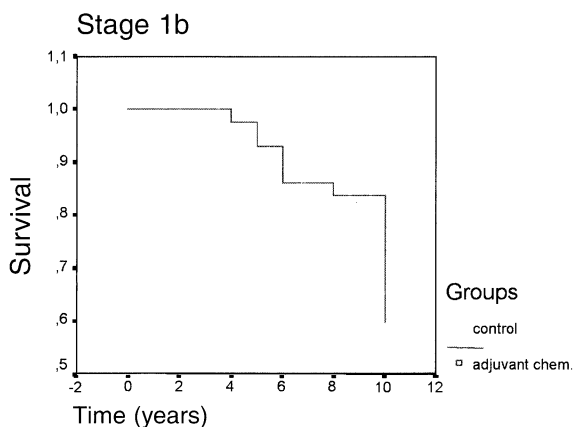


Figure 2. — Overall survival according to FIGO stage.

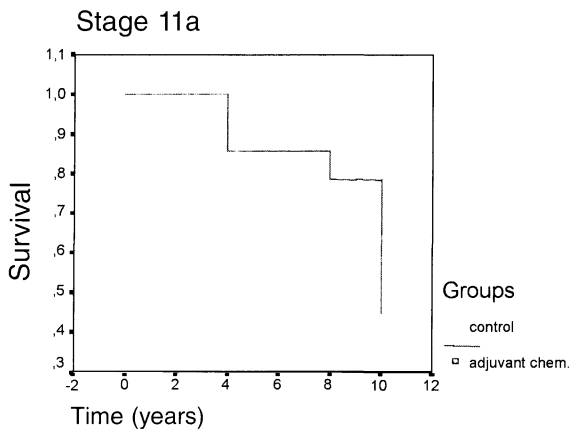


Figure 3. — Overall survival according to FIGO stage.

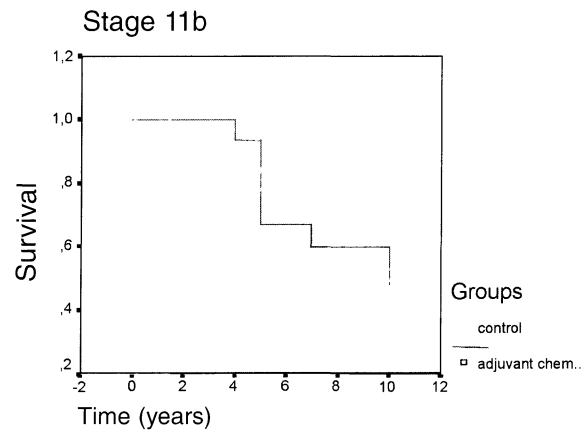


Figure 4. — Overall survival according to FIGO stage.

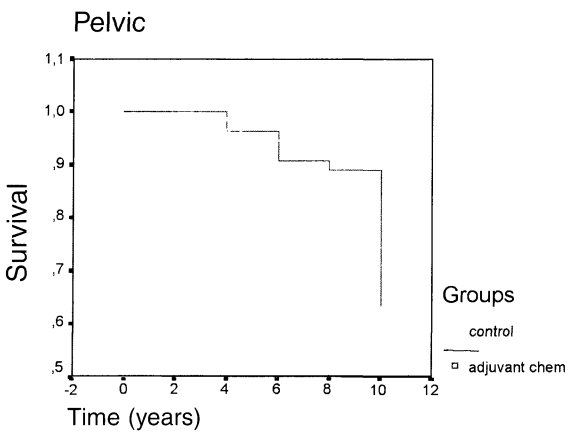


Figure 5. — Overall survival according to lymph-node status (site).

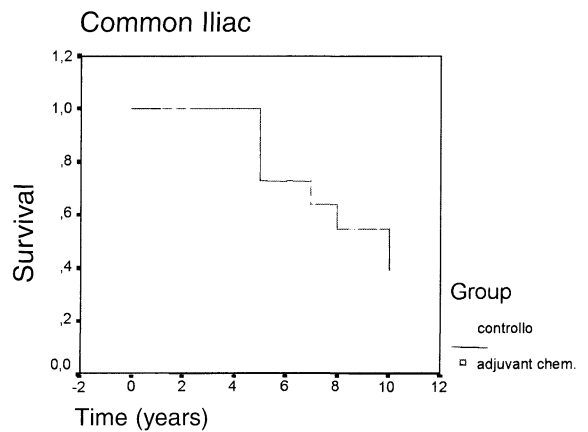


Figure 6. — Overall survival according to lymph-node status (site).

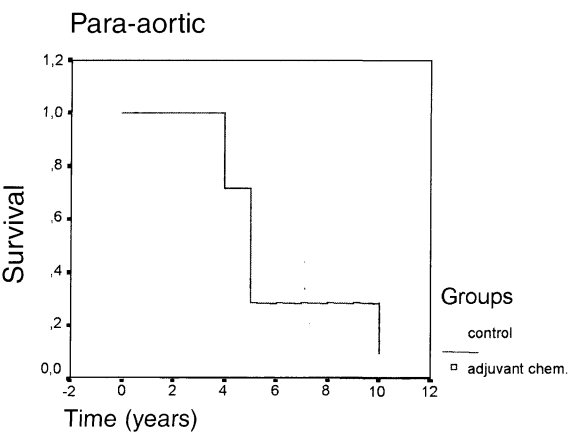


Figure 7. — Overall survival according to lymph-node status (site).

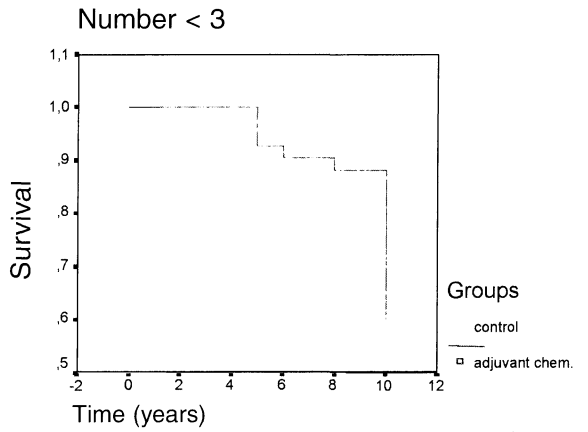


Figure 8. — Overall survival according to lymph-node status (number).

A similar consideration appears from a study of the comparative curves related to the number of positive lymph nodes (Figures 8 and 9), with better results for lymph-node positivity greater than two. In fact, in this

group survival was found to be 53.3 vs 41.2% (+12.1%) compared to 71.4 vs 65.9% (+ 5.5%) for lymph node positivity less than three with log rank = .30 and 1.91, respectively (p = NS).

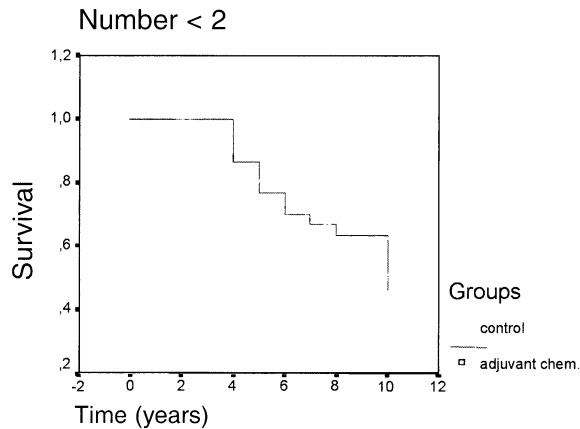


Figure 9. — Overall survival according to lymph-node status (number).

Discussion

The lower incidence of positive lymph nodes in patients suffering from squamous cell carcinoma of the cervix treated with neoadjuvant therapy [29], the poor efficacy of radiotherapy in the control of extrapelvic recurrences [15-30] and evidence of the progressive increase in efficacy of the new antineoplastic drugs [12-14] lead to the hypothesis of the usage of adjuvant chemotherapy in patients at high risk of recurrence for lymphnodal positivity. A study by Lay [6] on a group of women with positive lymph nodes demonstrated a statistically significant higher incidence of survival in patients treated with adjuvant chemotherapy (survival 75% vs 47%; $p = .05$). However, in a randomized trial, Tattersall *et al.* did not confirm the evidence of a beneficial effect in patients with positive lymph nodes treated with adjuvant chemotherapy [23].

The inconsistency of the data reported in the literature led the authors to verify the operative case history followed during 30 years of oncological activity [25-27].

The homogeneity of treatment and of selection of the patients made the cases more comparable statistically, whereas many institutes did not make a statistical evaluation of the different therapeutic strategies adopted in relation to the prognostic state [23].

The study was ended at a sufficient time to guarantee a satisfactory survival analysis (with a minimum period of observation of six years) compared to other data and other analyses reported in the literature [6]: survival was therefore evaluated after at least six years, so as to reduce the percentage of controls concluded too soon; in fact, such a limitation could have obscured the most important log-rank effect.

The decision to select the cases on the basis of surgical and not clinical staging is linked to the diagnostic certitude of the anatomicopathologic control. As early as 1972 Napolitano *et al.* [31] reported an incidence of errors of 24% on the clinical diagnosis of staging. Present-day diagnostic possibilities have reduced this margin but it can in any case be estimated at around 16% for under or over-staging.

Most analyses of the prognostic factors identified lymph-node metastasis and size of the neoplasia as the most important survival factors [6], however the age of the patients was found to be important in some studies. This parameter was therefore limited to 65 years to avoid excessive interferences linked to senile pathology. In reality, only 2.4% of the patients in the study died due to causes unrelated to the disease studied.

Radical surgery and integral lymphadenectomy [32] have been suggested by an analysis of the results to be linked to the surgical technique. In fact, the aim of selective lymphadenectomy is basically diagnostic.

A study [33] carried out by means of multivariate analysis revealed that several independent risk factors existed; we therefore selected patients on the basis of Figo stages and number and site of the positive lymph nodes.

In relation to the type of chemotherapy used, we must point out that all the therapeutic protocols demonstrate that cisplatin, vinblastine and neomycin can be safely administered and there is no evidence of excessive toxicity on the mucosae or the bone marrow [29-34].

The choice of the retrospective type of evaluation of the control group was imposed by the ethical need to guarantee, in any event, to the patients assigned to our center everything therapeutically valid for the purpose of controlling the disease [34, 35]. The reference cases related to the period 1961-79 were selected from women who would not or could not have adjuvant treatment after radical surgery. The selection criterion was homogeneity with the group being studied.

Even if the forced limitation of the number of cases treated did not permit optimum statistical reliability of the results obtained, the results nevertheless are consistent with the data found in the literature in reporting an improvement in survival ranging between 3% and 28% [6, 9, 23].

On a comparative statistical analysis, the overall data in terms of survival and disease-free interval show evidence of worsening of the prognosis as the staging advances, without significant differences between the two groups ($p = NS$). An examination of the global survival also shows a similar pattern to the foregoing ($p = NS$), but a constant better performance of the study group compared to the control group can be seen.

This constant approaches statistical significance when the graph related to lymph node positivity greater than two is examined.

Tattersall *et al.* noted no significant advantages with adjuvant chemotherapy but they only studied patients with lymph node positivity limited to the pelvis and not of the lumbo-aortic stations [23].

On the other hand, Sivanesaratnam *et al.* [20] reports a survival of 76% in cases with positive pelvic lymph nodes given adjuvant treatment compared to 60.3% in the cases without adjuvant treatment.

Although the prognostic improvement is not significant at a statistical examination, it can also be seen in the

analysis of the disease-free interval, in accordance with the findings of Lahousen [9] in the only similar randomized study. However, in his study the percentage of local recurrences suggests that chemotherapy does not have relevant effects on pelvic recurrences. However the problem with these studies is that they include patients with positive lymph nodes and with invasion of the lymphovascular spaces in order not to limit the number of cases with extensive involvement. Furthermore, the lumbo-aortic site of the lymph nodes is not taken into consideration.

Conclusions

The overall statistical comparison of survival in the group given adjuvant treatment shows no significant differences from the control group.

However, as reported in the literature, that there is an improvement in survival and disease-free interval estimated in the order of 9% has been observed, as well as a reduction in the incidence of metastasis (Figure 10).

These results were found to be better when the number of positive lymph nodes was greater than two, when the common iliac stations were affected and in stage IIb.

Lastly, the possibility must be considered that patients in whom recurrences occur after surgery and chemotherapy can be treated with radiation treatment, where chemotherapy is found to be inefficacious in patients already treated with surgery and adjuvant radiotherapy [36].

The limits imposed by radiotherapy in the prophylaxis of repetitive distance processes and the progressive increase in efficacy of the new chemotherapy drugs appear to constitute the basis for increasingly widespread pharmacological experimentation [12].

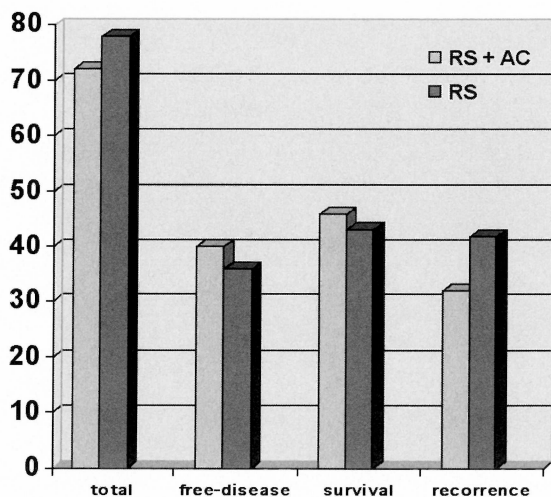


Figure 10. — Improvement in survival and disease-free period in the RS+AC group related to the RS only group.

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