Does FIGO clinical stage influence the survival of patients with early stages of uterine cervix carcinoma

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Summary

We studied the influence of the FIGO clinical stage on the prognosis of 114 patients with early stages of uterine cervix carcinoma who had been treated with radical surgery in the "La Fe" Maternity Hospital in Valencia between 1971 and 1989.

The prognosis became worse with each clinical stage, in line with the fact that the more advanced clinical stages are more likely to have certain types of spread, larger tumours and a greater stromal invasion depth.

However, the Cox regression adjustment of the variables predicting disease-free and survival intervals, including the clinical stage and preoperative and postoperative treatment, did not reveal a significant link between clinical stage and the prognostic indices studied, while postoperative treatment variables showed a great predictive capacity, possibly due to the fact that the postoperative treatment used in more advanced stages is more aggressive.

Key words: Clinical stage; Cervix cancer; Radical surgery; Prognosis.

Introduction

Cervical cancer is currently staged using the FIGO (International Federation of Gynaecology and Obstetrics) classification based on the 20th Annual Report and updated in 1995 [1]. Many publications have, however, documented differences between the clinical definition of Stages Ib and IIb and the histological classification of operation samples [2, 3].

The limits between Stages Ia and Ib were poorly defined until 1985 and limits of 1 mm, 3 mm, 4 mm and 5 mm have been proposed for microcarcinomas, as in the original Mestwerdt definition [4]. Only a few authors have proposed two or three dimensions and have set the volumetric limit of the carcinoma at 500 mm^3, which suggests future subdivisions of tumours limited to the cervix, as is shown in the updated FIGO staging of 1995 which foresees the division of Stage Ib into Ib_1 and Ib_2, depending on whether the tumour confined to the cervix is greater or smaller than 4 cm [1-5].

FIGO stages I and II reflect growth of the tumour more than the spread of the disease, leading to differences in the results of treatment in Stages I, II and III. The link between lymph node metastases and clinical stage is an objective measure of these differences, applied especially to Stages Ib and II [6].

Some authors, such as Werner-Wasik *et al.* [4] and Burghardt *et al.* [7], consider that tumour size and parametrial extension should be included in the FIGO clinical classification to predict prognosis more effectively.

The aim of this study was to examine the predictive capacity of the FIGO clinical stage in the prognosis of patients with early stages of uterine cervix carcinoma and to evaluate to what extent it is useful in judging the seriousness of the illness and making decisions about treatment.

Materials and Methods

A prospective study was carried out for all patients diagnosed with cervical carcinoma between 1971 and 1989, at a stage which allowed treatment by radical surgery in the Department of Oncological Gynaecology at the Maternity Hospital, "La Fe", in Valencia. All patients in the study were followed up for at least five years.

We studied the relationship of general characteristics such as age; family, personal, obstetric and gynaecological history, reason for consultation, physical and complementary examinations, surgical treatment using Wertheim-Meigs intervention (total radical hysterectomy with pelvic lymphadenectomy); preoperative treatment using preoperative radiotherapy or neo-adjuvant chemotherapy with vincristine, cisplatin and bleomycin; postoperative treatment using postoperative radiotherapy and pathology, with the patients' clinical evolution.

A total of 114 clinical histories was studied and used to compile a database using a computer program for data analysis, the SPSS (*Statistical Package for Social Sciences*) version 6.1 for Windows.

The mean age of the patients was 49.1 ± 10.6 years old (range from 27 to 76). The mean age at the menarche was 12.7 ± 1.5 years and at the menopause 47.6 ± 4.3 years in the 51 (44.7%) postmenopausal patients. Eight patients were classified as Stage Ia (7%), 61 as Stage Ib (53.5&), nine as IIa (7.9%) and 36 as IIb (31.6%). With surgical staging, six patients (6.1%) were Stage Ia, 65 (65.7%) Stage Ib, 14 (14.1%) Stage IIa and 14 patients (14.1%) Stage IIb. Those previously treated with chemotherapy and/or radiotherapy were not classified, as reduction in tumour size can alter the surgical stage. Preoperative treatment was given to 15 patients (13.2%), preoperative radiotherapy to five (4.4%) and neo-adjuvant chemotherapy to the remaining ten (8.8%). Postoperative radiotherapy was given to 62 patients. The patho-

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logy of operation samples revealed 86 (75.4%) squamous-cell carcinomas, 19 (16.7%) adenocarcinomas and nine (7.9%) mixed carcinomas. There were 55 (48.2%) well-differentiated carcinomas, 26 (22.8%) moderately differentiated carcinomas and 33 (28.9%) poorly differentiated carcinomas. There was invasion of capillary-like spaces (CLS) in 31 cases (27.2%), endocervix invasion in 56 (49.1%), endometrial invasion in 14 (12.3%), myometrial infiltration in 14 (12.3%) and vaginal invasion in 18 cases (15.8%). Parametrial invasion was present in 16 cases (14%) and infiltration of surgical margins was found in two cases (1.8%). Lymph node involvement occurred in 19 patients (16.6%) and ovarian involvement in three (2.7%). The mean tumor size as measured in the operation sample was 2.2 ± 1.3 centimetres and stromal invasion depth gave a mean result of 1.2 ± 0.7 centimetres. At the end of the study, 80 patients (70.2%) were alive and disease-free, three (2.6%) were alive with tumour and 31 (27.2%) had died. Overall survival to two years was 87.7%, to five years 72.8% and to ten years 51.4%.

Following a description of the variables studied (mean and standard deviation of quantitative values and relative percentages regarding qualitative values), mean disease-free and survival intervals were compared using the Student's t-test and variance analysis (ANOVA). Finally, survival curves were estimated using the Kaplan-Meier method and a multivariate analysis was carried out using the Cox proportional hazards method to make adjustments for other potential predictors of recurrence and death.

Results

The characteristics of the patients and their clinical stage at the moment of diagnosis are shown in Table 1. No significant differences were found in age with respect to clinical stage; histological type and grade of differentiation were uniformly distributed among the different stages; endocervix invasion, endometrial invasion and vaginal invasion occurred with greater frequency in the more advanced stages. Tumour dimensions and stromal invasion depth were lower in the early stages, tumour size, tumour-cervix quotient and stromal invasion depth were significantly lower in Stage Ia than in other stages. Tumour area was statistically smaller in Stage Ia than in stage IIa and tumour volume was greater in Stage IIb than in the other stages. Pre-operative treatment did not differ for the different stages, but patients in the more advanced stages were more frequently treated with postoperative radiotherapy.

The survival curves showed a progressive deterioration as the clinical stage advanced, for both disease-free and survival intervals (Figures 1 and 2), though the comparison of survival intervals for each stage (Table 2) and the analysis of survival adjusted clinical stage and for pre- and postoperative treatment (Table 3) showed no statistically significant relationships.

Table 1.— *Characteristics of patients in relation to clinical stage at the time of diagnosis.*

CLINICAL STAGE		IA	IB	IIA	IIB	P
Age	**≤ 40 years**	2 (25%)	15 (25%)	3 (33%)	4 (11%)	NS
	41-60 years	6 (75%)	39 (63%)	3 (33%)	25 (70%)	
	> 60 years	0	7 (12%)	3 (33%)	7 (19%)	
Surgical stage	**Ia**	5 (62%)	1 (2%)	0	0	**< 0.001**
	Ib	1 (13%)	45 (82%)	2 (22%)	17 (63%)	
	IIa	2 (25%)	5 (9%)	5 (56%)	2 (7%)	
	IIb	0	4 (7%)	2 (22%)	8 (30%)	
Histological type	**Squamous cell ca**	8 (100%)	44 (72%)	6 (67%)	28 (78%)	NS
	Adenoca	0	12 (20%)	2 (22%)	5 (14%)	
	Mixed ca	0	5 (8%)	1 (11%)	3 (8%)	
Grade of	**G1**	3 (37.5%)	31 (51%)	4 (44%)	17 (47%)	NS
Diferentiation	**G2**	2 (25%)	14 (23%)	1 (11%)	9 (25%)	
	G3	3 (37.5%)	16 (26%)	4 (44%)	10 (28%)	
CLS invasion		0	16 (26%)	3 (33%)	12 (33%)	NS
Endocervix invasion		2 (25%)	27 (44%)	8 (89%)	19 (53%)	**< 0.05**
Endometrial invasion		0	6 (10%)	4 (44%)	4 (11%)	**< 0.05**
Myometrial infiltration		0	5 (9%)	3 (33%)	6 (17%)	NS
Vaginal invasion		0	7 (11%)	4 (44%)	7 (19%)	**< 0.05**
Parametrial invasion		0	7 (11%)	1 (11%)	8 (2%)	NS
Nodal metastasis		0	9 (15%)	3 (33%)	8 (22%)	NS
Tumour size		0.6 ± 0.2	2.2 ± 1.1	3 ± 2,1	2.4 ± 1.1	**< 0.001**
Area		0.4 ± 0.3	4.8 ± 5.4	8.7 ± 13.4	5.8 ± 5.7	**< 0.05**
Volume		0.2 ± 0.2	6.4 ± 8.6	27.1 ± 52	12 ± 18	**< 0.005**
Tumour-cervix quotient		0.2 ± 0.04	0.3 ± 0.2	0.5 ± 0.2	0.4± 0.2	**< 0.001**
Depth of invasión		0.5 ± 0.2	1.1 ± 0.6	1.5 ± 1.2	1.4 ± 0.7	**< 0.001**
Preoperative treatment	**None**	8 (100%)	55 (90%)	9 (100%)	27 (75%)	NS
	Radiotherapy	0	2 (3.5%)	0	3 (8%)	
	Chemotherapy	0	4 (7%)	0	6 (17%)	
Postoperative treatment	**None**	8 (100%)	31 (51%)	3 (33%)	10 (28%)	**< 0.005**
	Radiotherapy	0	30 (49%)	6 (67%)	26 (72%)	

NS = not significant.

Table 2. — *Comparison of means (ANOVA) of the clinical stage variant with respect to disease-free interval and survival interval.*

DISEASE-FREE INTERVAL		MEAN ± DS (MONTHS)	F	DF	P
Clinical stage	**Ia**	90.1 ± 32.4	1.02	3;110	NS
	Ib	85.6 ± 54.7			
	IIa	66.3 ± 43			
	IIb	69.7 ± 51			
SURVIVAL INTERVAL		**MEAN ± DS (MONTHS)**	**F**	**DF**	**P**
Clinical stage	**Ia**	93.1± 33.6	1.03	3;110	NS
	Ib	91.5 ± 53			
	IIa	71.6 ± 48.3			
	IIb	75.6 ± 50			

NS = not significant; DF = Degree freedown.

Table 3. — *Cox regression equations for the variable clinical stage, preoperative treatment and postoperative treatment with respect to disease-free interval and survival interval.*

DISEASE-FREE INTERVAL		HAZARD RATIO	CI 95 %	P
Clinical stage	**Ia**	1	1	
	Ib	0.7	(0.4 - 1.5)	NS
	IIa	1.6	(0.7 - 3.8)	NS
	IIb	0.9	(0.4 - 2)	NS
Preoperative treatment	**none**	1	1	
	radiotherapy	6.2	(0.4 - 8.3)	NS
	chemoterapy	5.4	0.4 - 6.3)	NS
Postoperative treatment	**none**	1	1	
	radiotherapy	2.3	(1.4 - 3.7)	**< 0.001**
SURVIVAL INTERVAL		**HAZARD RATIO**	**CI 95 %**	**P**
Clinical stage	**Ia**	1	1	
	Ib	0.7	(0.3 - 1.4)	NS
	IIa	1.6	(0.6 – 4)	NS
	IIb	0.9	(0.4 – 2.1)	NS
Preoperative treatment	**none**	1	1	
	radiotherapy	0.8	(0.2 - 3.2)	NS
	chemoterapy	1.7	(0.6 - 4.4)	NS
Postoperative treatment	**none**	1	1	
	radiotherapy	2.1	(1.3 - 3.4)	**< 0.005**

CI = confidence interval; NS = not significant.

Discussion

The more advanced clinical stages are more likely to have certain types of spread, and tumour size and stromal invasion depth are lower in the earlier stages. These facts suggest that prognosis worsens as the clinical stage advances. However, it has not been demonstrated that the variables of clinical stage and preoperative treatment are related to disease-free and survival intervals.

For some authors, as for us, the different treatments used at the different clinical stages of tumour makes the survival of patients with Stages IIa and IIb identical and the survival of patients with Stages Ib and IIa fairly similar [8-11]. Coia *et al.* [12], like us, reported similar survival to five years for the early stages treated with radical surgery. Bolla [13] also shows similar survival to five and ten years for Stage Ib and for Stage IIa. Similarly, Finan *et al.* [2] and Grisby [3], with regard to the new FIGO staging definitions of 1995, consider that patients included in Stage Ib_2 have a lower survival to five years, compared to patients included in Stage Ib_1, although the new subdivision cannot be considered an independent factor influencing prognosis.

For other authors, however [14, 15], the clinical stage at the moment of diagnosis is one of the most important predictors of the evolution of the disease. The evolution of FIGO staging definitions and their modifications reflect this, increasingly defining the limits of each stage and individualising the treatment that must be used in each case [1]. In these studies, many patients are in Stage Ib, with survival being significantly higher in the early stages than for patients in Stages IIa and IIb [2, 3].

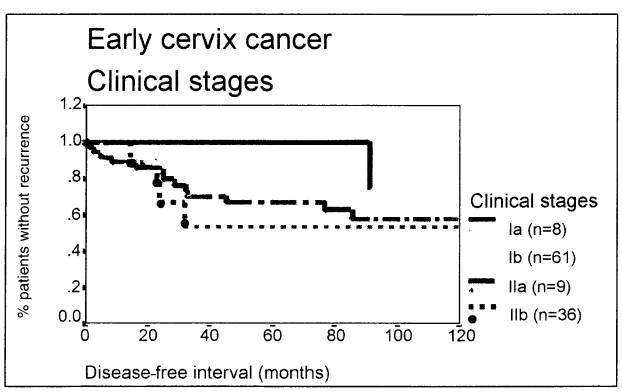

Figure 1. — Survival curve calculated using Kaplan-Meier method for **disease-free intervals** corresponding to **clinical stages**. **"Log rank" test** (5.48; df =3; p = NS).

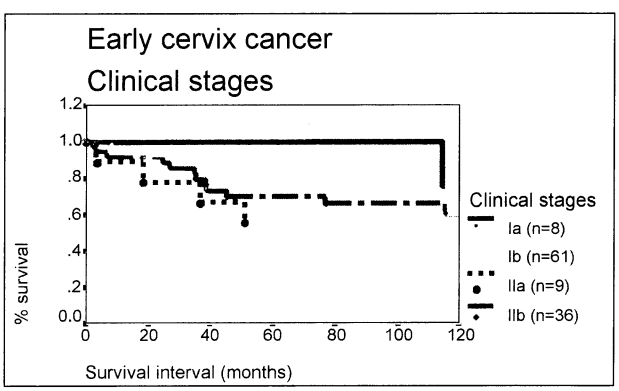

Figure 2. — Survival curve calculated using Kaplan-Meier method for **survival intervals** corresponding to **clinical stages**. **"Log rank" test** (5.47; df = 3; p = NS).

Kilgore *et al.* [16] and Pedersen *et al.* [17] found that clinical stage, tumour size and the presence of lymph node metastases were the most important prognostic factors.

A study of the literature relating to patients with cervical cancer and its evolution has revealed that survival percentages to five years for Stage Ib of cervical cancer vary from 72% (Werner-Wasik *et al.*) [4] to 93% (Inoue and Okumura in 1984) [6]. Like Zander *et al.* [18] and Monaghan *et al.* [19] we had a 5-year survival of 84%. Survival to five years for Stages IIa and IIb was 67% and 50%, similar to those found by Reddy *et al.* [20].

The incidence of lymph node metastases was 15% for Stage Ib, in agreement with Inoue and Okumura [6] and Kovalic *et al.* [21], and it was 33% for stage IIa, a slightly higher percentage than found by others [6-10], and 25% for stage IIb, somewhat lower than that reported by Inoue and Okumura (38%) [6] and Graz (45%) [10].

Conclusion

Clinical stage influences the prognosis and evolution of patients with early stages of uterine cervix carcinoma, though it is not related to survival intervals. As the clinical stage advances, the morphometric characteristics of the tumour suggest negative evolution and the prognosis worsens.

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