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Mariano Martin-Loeches · Rafael M. Ortí
Enrique Asins · Joaquin Llixiona

The prognostic implications of anaemia in the outcome of patients with early stages of uterine cervix carcinoma

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Abstract We studied the prognostic value of anaemia in the evolution of patients with early stages of uterine cervix cancer and treated with radical surgery. An observational study of 114 patients treated for cervical cancer at the "La Fe" Maternity Hospital in Valencia (Spain) during the period 1971 to 1989. Survival analyses were carried out whereby both recurrence and mortality rates were considered. The level of haemoglobin influences the prognosis of the patients in the study presented, and explains a variation in the disease-free interval in correlation with that of tumour size. However, its influence on the survival interval proved to be somewhat less. Its predictive value is not diminished when associated with other important factors regarding the influence on patient evolution and is seen to be a protector variable against recurrence. Patients with haemoglobin levels of less than 13 gr/dl have a less favourable prognosis and this prognosis worsens still further when levels are lower than 12 gr/dl, which is more frequently the case in patients under 40 years of age and with a greater stromal invasion depth. The influence of haemoglobin levels is equally as important in its influence on prognosis and patient evolution as the volume of the tumour itself. The effect of this variable depends on both the clinical characteristics of the patients and the pathological characteristics of the tumour.

Keywords Anaemia · Uterine cervix cancer · Early stage · Prognosis

M. Martin-Loeches · E. Asins · J. Llixiona
Service of Gynaecological Oncology,
Department of Gynaecology, "La Fe" University Hospital,
Valencia, Spain

R.M. Ortí
Service of Preventive Medicine, Clinic University Hospital,
Valencia, Spain

Mariano Martin-Loeches de la Lastra (✉)
Calle Abú-Zeyán, 8–10–2ª, 03700 Denia, Alicante, Spain
e-mail: mm-loeches@coma.es
Tel.: +34-965787894, Fax: +34-965780713

Introduction

Blood analyses of patients with cancer of the uterine cervix have been studied with the dual objective of determining if it would be possible to use any of their parameters as prognostic factors, and establishing an initial value from which an unfavourable evolution may be predicted [2, 4, 9, 12, 16, 18, 20].

Oxygenation has been associated with an enhanced tumour response to radiation. The recommended postradiation haemoglobin level should be of at least 10 g/dl [4, 20] and some researchers indicate that levels of 12 g/dl produce an improved outcome [18].

In Hirst's study [8] of the correlation between low haemoglobin and the response to radiotherapy and hyperbaric oxygen, he indicates that the duration and the severity of hypoxia constitute significantly important factors in determining cell survival, coinciding with the proposals put forward by various other authors [1, 5].

The evolution of patients with carcinoma of the cervix requiring postoperative radiotherapy depends in large on the grade of oxygenation of tumour tissue, hence good tumour vascularization and the use of blood transfusion in anaemic tumour patients give rise to an improved prognosis due to the resulting increase in the concentration of haemoglobin [3, 11, 17].

Evans and Bergsjo [4], Bush [2], Virago et al. [19] and Kapp [9] demonstrate that patients with anaemia suffer a higher rate of recurrent disease in the pelvis and reduced survival. Pathanapan et al. [12] and Stehman et al. [16] find no correlation between haematocrit and prognosis.

The objective of this work is to study the impact of anaemia on the prognosis and evolution of patients with early stages of cancer of the uterine cervix and to consider if this haematological parameter is sensitive to modification, in an attempt to obtain increased survival in these patients.

Table 1 General characteristics of the patients according to the variables included in the study and their respective statistics

		Mean ± SD (months)	N0	%	Survival interval	
					Mean ± SD (months)	p
General characteristics	Age (years)	49.1 ± 10.6				
	Menarche (years)	12.7 ± 1.5				
	Menopause (years)	47.6 ± 4.3	51	44.7%		
Stage	Ia		8	7%	93.1 ± 33.6	NS
	Ib		61	53.5%	91.5 ± 53	
	IIa		9	7.9%	71.6 ± 48.3	
	IIb		15	31.6%	75.6 ± 50	
Adjuvant treatment	Pre-operative radiotherapy		5	4.4%	96.2 ± 83.3	<0.05
	neo-adjuvant chemotherapy		10	8.8%	51.3 ± 24.9	
	postoperative radiotherapy		62	54.4%	62.3 ± 34.5	
Pathology	squamous cell cancer		86	75.4%	85 ± 48	NS
	adenocarcinoma		19	16.7%	84 ± 61.1	
	mixed carcinoma		9	7.9%	87.1 ± 58	
Grade of differentiation	well-differentiated		55	48.2%	88.2 ± 23	NS
	moderately differentiated		26	22.8%	78.3 ± 22.3	
	poorly differentiated		33	28.9%	68.4 ± 34.5	
Tumour characteristics	tumour size (cm)	2.2 ± 1.3				
	stromal invasion depth (cm)	1.2 ± 0.7				

NS = not significant; cm = centimetres.

Table 2 Comparison of means (t-test) for different groups of patients according to haemoglobin levels in the blood analysis (values in months)

		Mean ± SD (months)	t	df	p
Disease-free survival Interval					
Level of Hg (mgr/dl)	<12 mgr/dl	58,6 ± 41,6	12,8	1;113	<0,001
	≥12 mgr/dl	92,5 ± 53,2			
	<13 mgr/dl	65,1 ± 48,3	17	1;113	<0,001
	≥13 mgr/dl	103,8 ± 48,3			
Survival Interval					
Level of Hg (mgr/dl)	<12 mgr/dl	71,7 ± 47,3	5,11	1;113	<0,05
	≥12 mgr/dl	93,4 ± 51,2			
	<13 mgr/dl	72,6 ± 50,1	12,9	1;113	<0,001
	≥13 mgr/dl	106,2 ± 44,7			

Patients and methods

A prospective observational study was undertaken of all those patients diagnosed with a carcinoma of the cervix, at a stage which could be treated with radical surgery performed by the Service of Gynaecological Oncology of the Maternity Hospital "La Fe" in Valencia, during the period 1971 to 1989, and whose evolution could be followed up for a minimum of five years subsequent to radical surgery.

We studied the general characteristics of the patients according to age; family, personal, obstetric and gynaecological histories; motive of consultation; physical and concommitant examinations; surgical treatment with Wertheim-Meigs radical hysterectomy and pelvic lymphadenectomy; pre-operative treatment with radiotherapy or neo-adjuvant chemotherapy with vincristine, cisplatin, Bleomycin; postoperative treatment with radiation; pathology and evolution (Table 1).

At the end of the study the patients analysed in this work were classified as follows; 80 patients (70.2%) survived tumour-free, 3 patients (3.6%) survived yet the tumour persisted and 31 patients (27.2%) died. The 2,5 and 10-years global survival rates were of 87.7%, 72.8% and 51.4% respectively.

In total 114 sets of medical records were studied, from which a database was compiled to include the variables most relevant to prognosis. In order to obtain an analysis of the subjects studied, the mean and the standard deviation of the quantitative values together with the relative percentages of the qualitative variables were calculated. In order to study the effect of the different variables on disease-free and survival intervals, t-tests or analyses of variance (ANOVA), the chi-squared test and a multivariate analysis carried out using the Cox proportional hazards model were undertaken. The analysis of the data was carried out using the SPSS (Statistical Package for Social Sciences) Windows 6.1 version (Licence N0 707852).

Results

Using a multiple regression analysis which included all the variables of the bivariate statistical analysis, it was demonstrated that the disease-free interval depended on the haemoglobin (β=13.5; CI: 6.2–20.8) and fibrinogen (β=0.3; CI: 0.06–0.54). Furthermore, a statistically significant correlation was observed between the survival interval and haemoglobin (β=11; CI: 3.9–18.2) and fibrinogen (β=0.3; CI: 0.04–0.5). The haemoglobin level

Table 3 Patient characteristics in relation to blood analysis haemoglobin level

Haemoglobin		Hazard Ratio	Mean ±SD	p
Age	≤ 40 years	3,33	12,5 ± 1,4	<0,05
	41–60 years		13,4 ± 1,6	
	> 60 years		13,1 ± 1,4	
Clinical stage	Ia	0,19	13,3 ± 1,7	NS
	Ib		13,3 ± 1,7	
	IIa		13 ± 1,7	
	IIb		13 ± 1,4	
Surgical stage	Ia	0,32	12,8 ± 1,7	NS
	Ib		13,3 ± 1,5	
	IIa		13,5 ± 1,5	
	IIb		13,3 ± 1,6	
Histology type	Squamous	0,12	13,2 ± 1,6	NS
	Adenoca		13,3 ± 1,7	
	mixed ca		13,1 ± 1,5	
Grade of differentiation	G1	0,27	13,3 ± 1,7	NS
	G2		13,4 ± 1,6	
	G3		13,1 ± 1,5	
CLS invasion	yes	0,23	13,1 ± 1,6	NS
	no		13,2 ± 1,5	
Endocervix invasion	yes	3,28	13 ± 1,5	NS
	no		13,4 ± 1,6	
Endometrial invasion	yes	0,17	13 ± 1,6	NS
	no		13,2 ± 1,6	
Myometrial invasion	yes	0,23	13 ± 1,6	NS
	no		13,2 ± 1,6	
Vaginal invasion	yes	0,01	13,2 ± 1,2	NS
	no		13,2 ± 1,6	
Parametrial Invasion	yes	0,01	13,2 ± 1,6	NS
	no		13,2 ± 1,6	
Nodal Metastasis	yes	3,12	12,6 ± 1,5	NS
	no		13,3 ± 1,6	
Tumour size		–0,03		NS
Area		–0,04		NS
Volume		–0,06		NS
Tumour-cervix quotient		–0,01		NS
Invasion depth		–0,21		<0,05
Pre-operative treatment	None	3,05	13,3 ± 1,5	<0,05
	Radiotherapy		12,8 ± 2	
	Chemoterapy		12,1 ± 1,2	
Post-operative treatment	None	0,24	13,27 ± 1,7	NS
	Radiotherapy		13,12 ± 1,5	

NS = not significant

explains the variability rate of 18% in the disease-free interval and if the global level of haemoglobin and fibrinogen are taken into account, then the 25% rate of variability can also be explained. With regard to the survival interval, the 13% rate of variability could be accounted for by haemoglobin, whilst haemoglobin together with fibrinogen produced a variability of 20%.

Below a haemoglobin level of 13 gr/dl, both the disease-free and survival intervals decreased. When this level was set at 12 gr/dl of haemoglobin, the mean differences were reduced (Table 2).

On the other hand, in contrast to the effect of fibrinogen, haemoglobin showed a statistically significant correlation with patient age at the time of diagnosis, stromal invasion depth and the type of pre-operative treatment instituted (Table 3).

This association was maintained in the analysis using the Cox proportional hazards model, where haemoglobin, along with vaginal invasion and invasion of the capillary-like spaces, continued to be a significant factor regarding the disease-free survival interval. Nevertheless, in contrast to vaginal invasion and nodal metastasis, the level of haemoglobin could not be associated the survival interval (Table 4).

Discussion

Several publications have addressed the study of blood analyses of patients with carcinoma of the cervix in order to determine if parameters exist which can be used as prognostic factors and, if so, from which initial value an unfavourable evolution might be predicted [2, 4, 9, 12, 16, 18, 20].

Haemoglobin levels are related to patient prognosis in this study, thus explaining a variation in the disease-free survival interval in correlation with tumour volume, which leads to an interval increase of one year per milligram of haemoglobin. Its influence on the survival interval is somewhat less, giving rise to an increase of just

Table 4 Cox multivariate analysis of the significant variables of disease-free survival intervals (37 patients with tumour recurrence (32.5%) and survival intervals (31 patients died (27.2%)

		Hazard Ratio	CI 95%	p
Disease-free survival interval				
Age groups	≤ 40 years	1	1	
	40–60 years	0,8	(0,4–1,5)	NS
	> 60 years	1	(0,4–2,4)	NS
CLS invasion		2	(1,3–3,2)	<0,005
Endocervix invasion		1,4	(0,9–2,2)	NS
Vaginal invasion		2,2	(1,3–3,7)	<0,005
Parametrial invasion		1,3	(0,8–2)	NS
Tumour volume		1	(0,9–1)	<0,05
Invasion depth		4,3	(2–9,2)	<0,001
Postoperative treatment	None	1	1	
	Radiotherapy	0,9	(0,5 –1,2)	NS
Haemoglobin		0,7	(0,5–0,9)	<0,005
Fibrinogen		1	(0,9–1)	NS
Survival interval				
Age groups	≤ 40 years	1	1	
	40–60 years	0,7	(0,3–1,6)	NS
	> 60 years	0,9	(0,3–2,9)	NS
CLS invasion		1,4	(0,8–2,4)	NS
Vaginal invasion		1,9	(1,1–3,2)	<0,05
Nodal metastasis		1,7	(1–2,8)	<0,05
Invasion depth		3,8	(2–7,1)	<0,001
Postoperative treatment	None	1	1	
	Radiotherapy	0,5	(0,3–1,1)	NS
Haemoglobin		1	(0,7–1,3)	NS
Fibrinogen		1	(0,9–1)	NS
Recurrence		4,4	(1,9–10,5)	<0,001

CLS invasion = invasion of capillary-like spaces; CI = Confidence interval; NS = not significant

under one year. Its predictive value is not diminished when adjusted by other factors which have an important influence on patient evolution, and is shown to be a protector variable against recurrence.

Patients with haemoglobin levels of lower than 12 gr/dl are frequently under 40 years of age and have a greater stromal invasion depth. This extreme implies that if this level influences a particular prognosis, then it does so within the context of the clinical and pathological characteristics of the patients studied, and should not, therefore, be susceptible to modification directly before surgery in an attempt to improve patient evolution, because it constitutes a prognostic marker and not an independent factor.

Patients with haemoglobin levels lower than 13 gr/dl are prone to a less favourable prognosis, which is exacerbated further in patients with a haemoglobin level of lower than 12gr/dl, a theory which coincides with the observations made by Pederson et al. [13]. Several other authors indicate that haemoglobin levels of at least 10 gr/dl give rise to a favourable prognosis [4, 20], whilst others demonstrate that values of 12 gr/dl facilitate a better outcome [18].

Evans and Bersjo [4], Bush [2], Virago et al. [19], Kapp [9] and Werner-wasik et al. [21] demonstrate a greater incidence of recurrent disease in the pelvis and lower survival intervals in patients with carcinoma of the cervix and anaemia (haemoglobin less than 10–11gr/dl). Pathanapan et al. [12], Stehman et al. [16] and other authors [14], by contrast, find no statistically significant correlation between haematocrit and prognosis, although, as in this study, they indicate that there exists a greater survival rate to five years in patients with haematocrits between 35 and 45% and that this result is due to the relationship established between haematocrit and haemoglobin.

Fibrinogen levels have also proved to be influencing factors in the prognosis of the patients in this study, accounting for the slight variation in both the disease-free and survival intervals and increasing them by less than a month per point of its value. However, its prognostic value regarding the prediction of both survival and disease-free survival intervals is lost when applied to tumours of more important characteristics.

After reviewing literature on this subject matter, we find that Lee et al. [10] have observed that the cells of the human uterine cervix carcinoma biosynthesise fibrinogen and that this production plays an as yet unknown role in the prognosis of the disease. However, other authors do not include fibrinogen as a prognostic variable [4, 9, 12].

Rodriguez et al. [14] indicate that fibrinogen is related to thrombocytosis produced in tumour patients, although it is this latter characteristic which influences independently in a negative prognosis, as affirmed by Hernandez et al. [6]. These authors [7, 15] subsequently published that thrombocytosis found in patients with an unfavourable prognosis of cervical carcinoma is related to tumour volume and is not an independent prognostic factor.

In conclusion, both tumour volume and stromal invasion depth continue to constitute significant risk factors in recurrence, whilst the depth of invasion represents a factor in reducing the survival interval in the patients

studied. Equally, haemoglobin acts as a protective factor in the development of recurrence, despite losing statistical significance regarding the survival interval, as occurs in the case of fibrinogen with respect to both disease-free and survival intervals.

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