

## Research Article

# Evolution of the Incidence, Treatment, and Mortality of Cervical Cancer in Patients Treated at Miguel Servet University Hospital of Zaragoza

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## Abstract

Cervical cancer is the second most frequent gynecological tumor worldwide. The main reason for this frequency is not practicing adequate cytological screening. We performed a descriptive study of patients with invasive cervical cancer treated at our center from January 2003 through December 2015. In this period, 316 patients were diagnosed with cervical cancer. The mean age was  $54.39 \pm 16.20$  years, with a range of 19 to 90 years and a mode of 49 years. A total of 77.8% of the patients were Spanish and 22.2% were foreign. The initial treatment was surgical in 57.9% of the patients and radio-chemotherapy in 42.1%. The most frequent tumoral stage was IIB followed by IB1. The most common histological type was squamous carcinoma (61.3%), followed by adenocarcinoma (22.6%). Most of the patients, 64.2%, did not experience a relapse and overall survival was 64.9%. Notably, 86.30% of study subjects had not had an appropriate cervical cancer screening test.

**Keywords:** Cervical cancer; Chemoradiotherapy; Screening

## Abbreviations

HUMS: Miguel de Servet University Hospital, IACS: Aragon Institute of Health Sciences

## Introduction

After breast cancer, cervical cancer is the type of cancer with the highest incidence and mortality worldwide [1]. As many as 83% of cases of cervical cancer are diagnosed in developing countries, whereas it is less frequent in developed countries [2]. In Europe, cervical cancer ranks fourth among the most frequent types of cancer, and it is the seventh most common cause of mortality [3]. Although Spain is one of the European countries with a lowest incidence, two women die every day from cervical cancer despite the successful screening programs in place.

The primary goal of this study was to determine the incidence, therapy, relapse rate, and mortality of patients diagnosed with infiltrating cervical cancer treated in our hospital in the last 13 years to assess the evolution of these factors over time.

Secondary objectives included assessing the origin of referral, tumor stage, and more frequent histological types, and determine the efficacy of screening programs.

## Materials and Methods

The study was performed in the Miguel de Servet University Hospital (HUMS), which is located in Zaragoza, the fifth largest city of Spain. HUMS is a third-level hospital serving a population of 530,510 people. It is also the reference hospital for gynecologic oncology of the Autonomous Community of Aragon. Aragon has a population of 1,277,471 inhabitants, which accounts for 2.85% of the Spanish population. The total population of Zaragoza is 917,288 (71%

of the population of Aragon).

We conducted a retrospective review of patients diagnosed with cervical cancer and treated in our hospital from January 2003 to December 2015. During the study period, a total of 316 women were diagnosed with cervical cancer.

All patients with a diagnosis of infiltrating cervical cancer established in our Unit or elsewhere during the study period were included in the study.

Patients with high-grade cervical lesions or diagnosed in situ were excluded from the study.

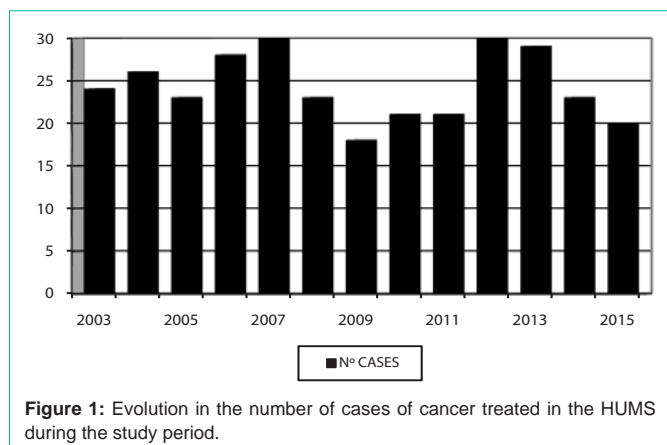
The sample was extracted from the database of the Unit of Gynecologic Oncology, where all patients diagnosed with cervical cancer from 2003 and treated in our Unit are registered. The clinical records of the patients included in the study were reviewed on a case-by-case basis upon request to the Service of Clinical Records.

For statistical analysis, the data obtained were transcribed into a computerized database using the IBM Statistics Process Social Sciences 15.0 package for Windows (Copyright© SPSS Inc., 2006 license owned by the University of Zaragoza).

We established a level of statistical significance with a p value < 0,05.

## Results

The incidence of cervical cancer in our hospital (HUMS) has remained stable since 2003. From January 2003 to December 2015, a total of 316 patients with a diagnosis of cervical cancer were treated in our center. Figure 1 shows the number of patients treated in our center during the study period.



**Figure 1:** Evolution in the number of cases of cancer treated in the HUMS during the study period.

**Table 1:** Origin of referral of the patients of the study.

CENTERS OF REFERRAL		
OUR HEALTH DISTRICT	247	78,2 %
OTHER HEALTH DISTRICTS OF THE PROVINCE	65	20,6%
OTHER COMMUNITIES	3	0.90%
OTHER COUNTRIES	1	0.30%

**Table 2:** First-line therapy by year.

	THERAPY BY YEAR				
	TOTAL	SURGICAL		NON-SURGICAL	
2003	24	12	50%	12	50%
2004	26	21	80.80%	5	19.20%
2005	23	11	47.80%	12	52.20%
2006	28	15	53.60%	13	46.40%
2007	30	15	50%	15	50%
2008	23	15	65.20%	8	34.80%
2009	18	13	72.20%	5	27.80%
2010	21	15	71.40%	6	28.60%
2011	21	9	42.90%	12	57.10%
2012	30	18	60%	12	40%
2013	29	16	55.20%	13	44.80%
2014	23	16	69.60%	7	30.40%
2015	20	7	35%	13	65%

The mean age at diagnosis was 54.39 ± 16.20, ranging from 18 to 90 years, with a mode of 49 years. Only five patients (1.58%) were younger than 25 years at diagnosis.

As to the origin of referral of the patients included in the study, 247 (78.2%) were referred from other gynecology services or gynecology emergency units of our health district, and 69 (21.8%) were referred from other hospitals of the Community of Aragon, other provinces of Spain and even other countries (see other countries in Table 1). By nationality, 246 (77.8%) were Spanish, 70 (22.2%) were from other countries.

First-line therapy was surgery in 183 patients (57.9%), and radiotherapy and/or chemotherapy in 133 (42.1%) patients. Table 2

**Table 3:** Tumor stages in study subjects.

TUMOR STAGE		
STAGE	No.PATIENTS (%)	%
IA1	45	14.2
IA2	12	3.8
IB1	80	25.3
IB2	29	9.2
IIA	23	7.3
IIB	88	27.8
IIIA	19	6
IIIB	9	2.8
IIIC	1	0.3
IV	9	2.8
GROUP III (SARCOMA)	1	0.3

displays the first-line therapy administered to patients by year.

Indications for surgery were based on tumor stage and size. Patients with a tumor stage ≥ IIB and locally advanced tumors > 4cm were not considered candidates for surgery. Only one patient refused to undergo surgery despite being a candidate. Surgery was contraindicated in two cases due to comorbidities.

The most common stage was IIIB, followed by IB1. Table 3 shows the different tumor stages established in study subjects.

The most common type of surgery was Wertheim-Meigs operation (97 cases) followed by hysterectomy with single or double annexectomy (18) and, to a lesser extent, other types of surgery. In 2011, all procedures were performed by laparotomy. From 2012, selected cases were treated surgically by laparoscopy.

The Wertheim-Meigs operation was first performed by laparoscopy in our Unit in 2013. Since then, six patients have undergone this procedure uneventfully. This procedure made it possible to reduce hospital stay by 5.2 days, which is a significant reduction with respect to procedures by laparotomy p=0.007.

The Selective Sentinel Node Biopsy (SLNB) technique started to be employed in our unit for cervical cancer at the end of 2013. Since its introduction, eight patients have undergone it plus a lymphadenectomy during the same procedure, as this technique has not been validated yet. The rate of intraoperative identification of the sentinel node was 100%, with no false positives and 100% specificity.

**Table 4:** Histological types according to the final anatomy-pathological study.

FINAL HISTOLOGICAL TYPE		
TYPE	No.PATIENTS	%
NO TUMOUR	26	8.2
CA. IN SITU	3	0.9
CA. SQUAMOUS	204	64.6
ADENOCARCINOMA	68	21.5
CA. SQUAMOUS ADENOCARCINOMA	1	0.3
OTHER HISTOLOGICAL TYPES	14	4.4

\*No tumour: micro-infiltrating tumour extirpated by cone-biopsy without surgical specimen.

**Table 5:** Tumor size.

TUMOR SIZE		
SIZE	Nº.PATIENTS	%
MICRO-INFILTRATING	82	25.9
1CM	36	11.4
2CM	31	9.8
3CM	36	11.4
4CM	39	12.3

**Table 6:** Degree of differentiation.

DEGREE OF DIFFERENTIATION		
G	Nº.PATIENTS	%
G1	70	16.8
G2	153	48.4
G3	40	12.7
UNKNOWN	53	16.8

**Table 7:** Lymphovascular invasion in study subjects.

LYMPHOVASCULAR INVASION		
ILV	Nº.PATIENTS	%
SI	114	36.1
NO	98	31
UNKNOWN	104	32.9

Epidermoid carcinoma was the most frequent (220 (69.6%) tumor histology at baseline examination based on biopsy material or conization. These results were consistent with those of the final histological study, where epidermoid carcinoma kept being the most common histological type (204 (64.6%). Table 4 shows the final histological diagnoses for the study subjects.

Apart from histological type or tumor stage, other important factors associated with the risk of relapse determine the choice of first-line or complementary therapy, including tumor size, histological grade, or the presence or not of lymphovascular invasion. Tables 5-7 include a summary of the results obtained.

Tables 8-9 shows the complementary therapies administered after surgery and the treatments given to patients who did not undergo first-line surgery. All therapies were selected by the multidisciplinary team of gynecologic oncology based on tumor stage and factors associated with low, medium or high risk of relapse.

Most patients (64.2%) did not experience a relapse. Of the remaining patients, 19% had a relapse, 14.3% had tumor persistence, and 2.5% were lost to follow-up. The mean time to relapse was 20.63 ± 15.94 months, with a range from 3 to 84 months and a mode of 24 months.

Overall survival was 64.9%. The last follow-up visit was in March 2016. Mortality was 32%. Outcome is unknown for 3.2% of patients due to address change. Regarding mortality, 88.2% died from cervical cancer, whereas 11.8% died from other causes. The mean time to relapse was 31.46 ± 25.79 months, with a range from 2 to 120 months and a mode of 36 months. Table 10 shows overall survival by tumor stage. Notably, 86.30% of study subjects had not done an appropriate

**Table 8:** Therapy administered following surgery.

183 FIRST-LINE SURGICAL PATIENTS (57.9%)	COMPLEMENTARY THERAPY AFTER SURGERY		
	NONE	106	57.92%
	RADIODTHERAPY	35	19.12%
	CHEMOTHERAPY	4	2.19%
	RADIODTHERAPY + CHEMOTHERAPY	38	20.77%

**Table 9:** Therapy administered to non-surgical patients.

133 NO FIRST-LINE SURGICAL PATIENTS (42.1%)	ONLY A SINGLE THERAPY		
	NONE	0	0%
	RADIODTHERAPY	6	4.51%
	CHEMOTHERAPY	3	2.26%
	RADIODTHERAPY + CHEMOTHERAPY	116	87.22%
PALLIATIVE	8	6.01%	

**Table 10:** Overall survival by tumor stage.

OVERALL SURVIVAL	
STAGE	SURVIVAL %
IA1	100
IA2	91.7
IB1	95
IB2	68.97
IIA	65.22
IIB	54.55
IIIA	42.11
IIIB	33.34
IIIC	0
IV	0

cervical cancer screening.

## Discussion

The incidence of invasive cervical cancer is decreasing in most European countries due to screening programs, papilloma virus vaccine, and changes in the style of life of the population. Yet, it remains being a serious health problem [1-3].

There are 1,948 new cases of invasive carcinoma in Spain every year, with an approximate mortality of 721 patients per year. The incidence of this disease in Zaragoza is moderate to low, with 5.7 patients per 100,000 persons per year. Two women die from invasive cervical carcinoma every year in Spain [4].

We detected 316 patients diagnosed with invasive cervical carcinoma between January 2003 and December 2015. The year with the lowest incidence of cervical carcinoma was 2009, with 18 new cases, whereas the highest incidence was recorded in 2007 and 2012, with 30 new cases each. Although its incidence remained more or less stable during the study period, there was a rise in 2012 and 2013 with 30 and 29 new cases, respectively almost reaching the rate for 2007. Fortunately, from 2014, the number of new cases dropped again to 23 cases in 2014 and 20 in 2015.

The results show that first-line therapy was surgical in 57.9% of

cases and included radiotherapy and/or chemotherapy in 42.1%. Therapeutic decisions were primarily based on tumor stage, which is consistent with the results obtained by De Juanes et al. [5], who examined hospitalizations for cervical cancer in the Autonomous Community of Madrid between 1999 and 2002. Our results are also in agreement with SEGO guidelines for cervical cancer, which recommend surgery as the treatment of choice for early-stage cervical cancer (Evidence 1B. Consensus E), whereas radiotherapy plus chemotherapy are recommended for locally-advanced disease [6].

Our Unit was a pioneer in Spain in introducing electronic brachytherapy (May 2016) to treat non-operable residual tumors <3 cm in size following external radiotherapy.

Regarding the choice of first-line therapy, it is very important that histological reports include data on the presence or not of lymphovascular invasion, depth of the cervical stroma, and tumor size. These factors are essential for the estimation of the potential risk of relapse, as the depth of stromal invasion, lymphovascular invasion, and a tumor size > 4cm are considered poor presurgical prognostic factors. Postsurgical histological criteria for moderate risk of relapse include the presence of at least two of the following elements: tumor size >4 cm, deep stromal infiltration (>1/3 of the stroma) or lymphovascular invasion [6,7,8].

According to Xie et al. [9], patients with tumor stages Ib or IIA, stromal invasion <1/3, no lymphovascular invasion, and squamous histological type will benefit from a less aggressive surgery, as they are less likely to have parametrial invasion.

In our opinion, further efforts should be made to reduce the incidence of this serious disease. The natural course of this disease is well understood, and early detection is essential to prevent progression. Screening of healthy subjects has reduced the incidence and mortality of cervical cancer by up to 80-90% [10,11].

Screening programs for cervical cancer are not being currently implemented at national level, but at regional level. Thus, each autonomous community has developed its own screening program. Most screening programs are opportunistic, with suboptimal coverage and deficits in equity and efficacy. More than 60% of patients diagnosed with cervical cancer in Spain have never had a screening test.

In agreement with the “European Guidelines for Quality Assurance in Cervical Cancer Screening” [12,13], implementing a population screening program for cervical cancer should be a priority [14]. In the light that 86.30% of study subjects had never had an effective screening test, our Unit is trying that women undergo screening appropriately and, following the SEGO guidelines published in 2014 [12], we are trying that a population screening program is implemented in our health district.

Although the HPV vaccine is expected to reduce the incidence of cervical cancer dramatically, results won't be apparent until all the population that received the vaccine reaches 65 years of age, the age at which screening will be completed which will occur within 30 years. Therefore, from our perspective, economic and planning efforts should be made to implement a population screening program aimed at reducing mortality associated with this disease. In terms of cost-

effectiveness, the cases prevented added to early detected cases would make up for the cost of the implementation of a preventive program.

We also agree with SEGO on the recommended age for undergoing a screening test [12] 25 years, given that only 1.58% of patients were younger than 25 years at diagnosis, and most were related to rare histological types such as adenocarcinomas or sarcomas, for which the sensitivity of cytologies is low.

## Conclusions

Although sensitive screening tests are available for cervical cancer, this disease remains being a problem in Spain and, more specifically, in Aragon. Efforts should be made to ensure that patients undergo screening tests appropriately.

- The incidence of this disease remains stable, although a rise occurred in 2012 and 2013.
- The most frequent histological type is squamous carcinoma.
- First-line therapy for most patients was surgery, although 40% of tumors were non-operable due to an advanced stage or locally advanced stage.
- Inoperable tumors were prevalently treated with chemotherapy plus radiotherapy with radical intent.
- There has been a paradigm shift in the surgical approach to cervical cancer. At present, minimally invasive procedures performed by endoscopy are given preference and the BSGC technique is being progressively introduced.
- Electronic brachytherapy in non-surgical patients at baseline with a residual tumor size of < 3cm after external radiotherapy is a promising low-risk technique that requires a lower number of RT sessions.
- Women should be encouraged to undergo appropriate screening tests. The incidence of cervical cancer can be reduced by the implementation of large-scale population screening programs.

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