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ARTÍCULO ORIGINAL

Radiotherapy outcomes in patients with locally advanced cervical carcinoma and previous hysterectomy: a retrospective analysis

Resultados obtenidos con radioterapia en pacientes con carcinoma de cuello uterino localmente avanzado e histerectomía previa: un análisis retrospectivo

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Abstract

Objective: This study aims to assess the proportion of inappropriate hysterectomies and their subsequent impact on patients with cervical cancer admitted to our Radiotherapy Unit.

Methods: A retrospective cohort study was conducted using data extracted from medical records at the *Hospital Oncológico Solón Espinosa Ayala* (SOLCA) (Quito, Ecuador) between 2012 and 2015. A systematic review of hospital records identified instances of inadequate surgery, encompassing both simple hysterectomies for stages IB2 to IIA and any hysterectomy type for stages IIB or higher. Comprehensive data were accurately collected, including demographic information, histology, postoperative diagnostic investigations, and postoperative management. Patient follow-up was meticulously recorded to track occurrences of recurrence, progression, or death up to five years after treatment conclusion.

Results: A total of 641 patients diagnosed with cervical carcinoma and referred for chemoradiotherapy were identified; 81 patients (12.8%) referred in stages IB2 to IVA met the criteria for inadequate hysterectomy, with 11 patients (13.6%) showing residual lesions and 12 patients (14.8%) having positive margins. The mean overall survival (OS) of patients with inadequate hysterectomy was 77.5 months ($CI_{95\%}$ =69.3-85.7), with a median disease-free survival (DFS) of 92 months ($CI_{95\%}$ =65.5-118.4 months); 19 patients (23.4%) succumbed to the disease. Notably, patients with residual disease exhibited the worst OS and DFS outcomes.

Conclusions: A representative group of cervical cancer patients referred to the Radiotherapy Unit underwent inadequate hysterectomy. Within this group, patients with residual disease had worse oncological outcomes.

Keywords: uterine cervical neoplasms, hysterectomy, radiotherapy.

Resumen

Objetivo: Estudiar la proporción de histerectomías inadecuadas y su impacto en las pacientes con cáncer de cuello uterino ingresadas en la Unidad de Radioterapia.

Métodos: Se realizó un estudio de cohorte retrospectivo utilizando datos de los registros hospitalarios del Hospital Oncológico Solón Espinosa Ayala (SOLCA), Quito, Ecuador, entre 2012 y 2015. Se revisaron sistemáticamente las historias clínicas para identificar casos de cirugía inadecuada. Se consideraron cirugías inadecuadas, histerectomías simples para IB2 a IIA, así como cualquier tipo de histerectomía en estadios IIB o superiores. Se recopiló información demográfica, histológica, de investigaciones diagnósticas posoperatorias y del manejo posoperatorio. Se registró el seguimiento de las pacientes hasta la recurrencia, progresión o muerte cinco años después de finalizar el tratamiento.

Resultados: Se encontraron 641 pacientes diagnosticadas con carcinoma de cuello uterino remitidas para quimiorradioterapia, el 12,8% (*n*=81) de ellas en estadios IB2 a IVA, que cumplían criterios de histerectomía inadecuada. Once pacientes fueron derivadas con lesión residual y 12 pacientes con margen positivo. La supervivencia global (SG) media de las pacientes con histerectomía inadecuada fue de 77,5 meses (IC_{95%}=69,3-85,7), con una mediana de la supervivencia libre de enfermedad (SLE) de 92 meses (IC_{95%}=65,5-118,4); 19 pacientes murieron. Se encontró peor SG y SLE en el grupo de pacientes con enfermedad residual.

Conclusión: Un grupo representativo de pacientes con cáncer de cuello uterino derivadas a la unidad de radioterapia han sido sometidas a una histerectomía inadecuada. En este grupo de pacientes, aquellas con enfermedad residual tuvieron peores resultados oncológicos.

Palabras clave: neoplasias del cuello uterino, histerectomía, radioterapia.

Introduction

Cervical cancer ranked second in cancer incidence and mortality among women in Ecuador in 2020 (<u>1</u>). However, data from the National Tumor Registry revealed a 5-year survival rate of only 55.0% for women with cervical cancer during 2010-2014, which is lower than the figures reported in the literature (<u>2</u>). This disparity is likely because 46.0% of patients were diagnosed at advanced disease stages (<u>2</u>,<u>3</u>).

Most patients with cervical cancers in low-and middle-income countries present with the disease at stages that require radiation, and more than 50.0% of cancer patients requiring radiotherapy in these countries lack access to treatment ($\underline{3}$).

The management of each case should rely on accurate disease staging $(\underline{4}, \underline{5})$. Early-stage cervical cancer can often be cured with surgery. However, in locally advanced stages, the approach involves concurrent chemoradiation, followed by brachytherapy ($\underline{4-6}$). A simple hysterectomy without lymph node dissection is not a curative option for early disease stages, nor is surgery alone for advanced stages ($\underline{7-9}$). Improper utilization of these techniques poses a significant issue in certain regions, leading to inadequate treatment and inferior survival rates ($\underline{10-11}$). Several studies have

explored the percentage of cervical cancer patients who undergo unsuitable surgery, revealing varying proportions $(\underline{8},\underline{10-11})$. Inadequate preoperative assessment and false-negative pap smear results have been identified as potential reasons for inappropriate surgeries $(\underline{11},\underline{12})$.

Postoperative sequelae and the absence of a uterus limit the ability to achieve adequate dose delivery, especially in brachytherapy, which may be the reason for poor survival (10,11). In addition to impacting treatment delivery, these surgeries could negatively affect patient quality of life (11).

To evaluate the prevalence of inadequate hysterectomies in cervical cancer patients, this study aimed to investigate the proportion of such cases among those admitted to the Radiotherapy Unit and to report their corresponding oncological outcomes.

Materials and methods

After obtaining approval from the institutional Research Ethics Committee, a retrospective cohort study was conducted at the *Hospital Oncológico Solón Espinosa Ayala* (SOLCA), which is an oncological hospital in Quito, Ecuador. The study included patients admitted to the institution from 2012 to 2015, based on the following inclusion criteria: age over 18 years at diagnosis, clinical stages IB2 to IVA according to the eighth edition of the AJCC, and referral to the Center for Chemoradiotherapy. To be included in the study, patients must have undergone at least one simple contrast-enhanced computed tomography (CT) scan of the pelvis and abdomen for staging. Exclusion criteria encompassed patients who did not complete the prescribed treatment regimen, individuals with incomplete data regarding the surgical procedures, and cases diagnosed with sarcoma and neuroendocrine tumors.

The medical records of eligible patients underwent a systematic review to identify instances of inadeguate surgery. They included simple hysterectomies for stages IB2 to IIA, as well as any form of hysterectomy for stages IIB or higher. Data on demographics, surgical procedures, histology, postoperative diagnostic investigations, and postoperative management were extracted from the hospital register. Pathological data and details about radiotherapy and chemotherapy management were retrospectively reviewed in the clinical records. All data that did not appear in our primary source of information, such as degree of differentiation, state of the margins, number of nodes, lymphatic invasion, vascular invasion, etc., were collected through a review of the histopathological reports of the centers where the hysterectomies were performed.

Hysterectomies were classified according to the postoperative specimen's revisions at our institution and the disease status at referral, following the approach proposed by Andras et al. in 1973 and updated by Saibishkumar et al. in 2005 (8). Group 1 patients had microscopic evidence of invasive disease found incidentally at hysterectomy. Group 2 patients had gross tumors on the surgical specimen with apparent surgical clearance. Group 3 patients had positive margins without gross residual disease. Group 4 patients had one of the following characteristics or any combination: gross residual disease postoperatively, positive biopsy at admission, clinical evidence of residual or recurrent disease, and referred at <6 months postoperatively. Group 5 patients had the same features as Group 4 but were referred at >6 months postoperatively.

Information on local control was collected three months after the completion of treatment and evaluated using clinical, imaging. or histopathological criteria. Patient follow-up was recorded until recurrence, death, or five years after the conclusion of treatment. Recurrence data were obtained through physical examination, techniques, and/or imaging biopsy. Local recurrence was determined as detection of the disease on the vaginal vault or pelvic lymph nodes. Meanwhile, relapses in the para-aortic nodes or any place outside the pelvis were considered distant recurrences. Time to recurrence was calculated from the last brachytherapy session to the first evidence of recurrence.

For descriptive statistics, mean, mode, and median values were calculated. Also, standard deviation (SD) and interguartile range were estimated as measures of dispersion. Kaplan-Meier analysis was used to calculate overall survival (OS) as the time from the date of diagnosis to the date of death from any cause or the date of last follow-up. For comparisons between groups, a log-rank test was employed. Disease-free survival (DFS) was calculated as the time from the date of surgery to illness recurrence, with patients censored at the last follow-up if no disease recurrence occurred. Statistical significance was determined with a p-value less than 0.05 for all calculations. Data analysis was performed using the SPSS version 22 statistical package.

Results

A total of 641 patients were diagnosed with cervical carcinoma and referred for chemoradiotherapy; 92 of them had a previous hysterectomy. Of those 92 patients, 11 were excluded for incomplete data that did not allow us to establish the adequacy of hysterectomy. Thus, 81 patient (12.8%) referred in stages IB2 to IVA met the criteria for inadequate hysterectomy.

The median age of these patients was 48 years, ranging from 27 to 81. Following retrospective staging, 49 patients (60.4%) were classified as IIB or higher. Table 1 displays the T stages and histological lineage.

Table 1. Clinical features of hysterectomized patients (N=81)

Variable	Categories	n (%)
Clinical stages	IB	8 (9.9)
	IIA	16 (19.8)
	IIB	16 (19.8)
	IIIA	1 (1.2)
	IIIB	30 (37.0)
	IVA	2 (2.5)
	Х	8 (9.9)
Tumor stage	T1A1	1 (1.2)
	T1B1	12 (14.8)
	T1B2	10 (12.3)
	T1B	1 (1.2)
	T2A	16 (19.8)
	T2B	23 (28.4)
	T2	1 (1.2)
	Т3	7 (8.6)
	ТХ	10 (12.3)
Histologic type	Squamous	55 (67.9)
	Adenocarcinoma	20 (24.7)
	Adenosquamous	5 (6.2)
	Other	1 (1.2)
Differentiation	Well differentiated	5 (6.2)
	Moderately differentiated	62 (76.5)
	Poorly differentiated	10 (12.3)
	Unknown	4 (4.9)

Regarding the type of hysterectomy, 22 patients (27.2%) underwent simple hysterectomy, while 59 patients (72.8%) had radical hysterectomy. Lymph node dissection was conducted in 49 patients (60.5%), while 32 patients (39.5%) did not undergo node dissection. The median number of nodes resected was 4, with an interguartile range of 10.

<u>Table 2</u> presents the comprehensive classification of patients, taking into account the slide review findings of postoperative specimens and their disease status at referral following the updated Andras *et al.* approach ($\underline{8}$), as outlined in the methodology section. Notably, 11 patients (13.6%) were referred with residual lesions, while 12 patients (14.8%) exhibited positive margins without evidence of residual disease. **Table 2.** Number of patients in each group according the Andras *et al.* criteria updated by Saibishkumar *et al.* (8)

	Criteria	n	%
1.	Microscopic evidence of invasive disease found incidentally at hysterectomy	2	2.5
2.	Macroscopic evidence of a tumor in the surgical sample with apparent surgical clearance	56	69.1
3.	Positive margins without macroscopic re- sidual disease	12	14.8
4.	One of the following or any combination: macroscopic residual disease after sur- gery, positive biopsy on admission, clinical evidence of residual disease or recurren- cy, and remitted to radiotherapy within 6 months after surgery	8	9.9
5.	Same characteristics of patients as in Group 4 but remitted to radiotherapy more than 6 months after surgery	3	3.7

The median time to begin radiotherapy treatment after hysterectomy was 17 weeks, with a minimum of 6 and a maximum of 174 weeks. In total, 45 patients (55.5%) received concurrent chemotherapy and radiotherapy. Regarding radiotherapy, 77 patients (95.0%) received pelvic radiotherapy, whereas 4 patients (5.0%) underwent pelvic and para-aortic radiotherapy. Brachytherapy was carried out in 71 patients (87.7%), while 10 patients did not receive this treatment. The median time of total treatment duration was 12 weeks, with a minimum of 8 and a maximum of 24 weeks.

Treatment response was assessed 90 days after treatment termination in a cohort of 61 patients, with 9 having residual disease at treatment outset. Among these 9 patients, 4 achieved a complete treatment response, 1 had a partial response, 3 presented with stable disease, and 1 experienced disease progression. Conversely, among the remaining 52 patients who did not have residual disease at treatment initiation, 48 (92.3%) maintained disease-free status, while disease progression was observed in 4 patients.

In terms of overall survival (OS), 19 patients (23.4%) died; the median OS was unreached, with a median follow-up time of 43 months. The mean OS was 77.5 months ($CI_{95\%}$ =69.3-85.7) (figure 1). Disease-free survival (DFS) was assessed over a median follow-up time of 37 months. The median DFS was 92 months ($CI_{95\%}$ =65.5-118.4) (figure 1).



Figure 1. Overall survival and disease-free survival

Figure 2 shows OS and DFS comparisons between patients with and without residual disease (Groups 4 and 5) after surgery. The worst OS and DFS were found in the group of patients with residual disease; however, this difference was statistically significant only for OS.



Figure 2. Comparative overall survival and disease-free survival rates

Discussion

In 2020, Ecuador ranked among the top ten countries in Latin America with the highest incidence and prevalence of cervical carcinoma. Specifically, cervical carcinoma represented the fourth cause of oncologic mortality in Ecuadorian women (2,3). These high incidence and mortality rates could be attributed to limited access to preventive medicine in the oncological field (13).

Contrary to a clear indication for hysterectomy in early-stage cervical cancer, which has been subject

to investigations of diverse surgical techniques (14), radical hysterectomy is reserved for treating locally advanced cervical carcinoma in cases where patients are ineligible for brachytherapy after chemoradiotherapy or as a salvage treatment for recurrence (6-7,9).

To the best of the authors' knowledge, as of the publication date of this article, no reports are available on the clinical management of patients with locally advanced cervical carcinoma who had hysterectomy before receiving the recommended treatment of concurrent chemoradiotherapy in Latin America. Although neoadjuvant schemes have been explored for certain locally advanced stages to facilitate surgical intervention, they have not demonstrated a definitive benefit compared to radical management with chemoradiotherapy followed by brachytherapy (15).

On the other hand, the management of patients with tumor persistence after chemoradiotherapy or subsequent relapse or progression is complex. Despite ongoing clinical trials studying antineoplastic drugs like pemetrexed or topotecan as second-line treatment, the prognosis for such patients remains unfavorable (<u>16,17</u>). This is consistent with the mortality rates observed in patients with tumor persistence, as reported in our study.

In general, the 5-year overall survival rate for locally advanced cervical carcinoma treated according to international guidelines ranges from 30.0 to 80.0% (5). In our study, out of 81 patients, we observed 19 deaths (23.4%), resulting in a 5-year survival rate of 70.0% within the same period. This finding aligns with the survival rates reported in the literature reviewed.

However, the present study reveals the existence of inadequate management of cervical cancer (inadequate hysterectomies) in 12.8% of the cases, a figure lower than that reported by Verma *et al.* (<u>11</u>) in their study conducted in India, who found 25.0% of inadequate surgeries, or even the report presented by Münstedt *et al.* (<u>12</u>) in Germany, who found 15.0% of this type of surgeries.

Regarding overall mortality, our study revealed a mortality rate of 23.4%. The group with the highest percentage of contribution to overall mortality was the one with macroscopic residual tumors, where this rate reached 50.0%. These values are lower than those reported by Hopkins *et al.* (<u>18</u>), who found an overall mortality of 32.0% in postoperative women with locally advanced cervical cancer. Similarly, this study evidences better outcomes when compared to those reported by Roman *et al.* (<u>19</u>), who found an overall mortality of 57.0%, which further increased to 75.0% in the group of patients with macroscopic residual tumors after surgery.

Although these data may seem encouraging in this case, it is fundamental to consider that the literature consulted, except for the Indian study, was conducted in the 1990s and early 2000s, when technologies and access to radiotherapy were not as advanced as they are today. It is relevant to highlight the decline in OS observed in patients with macroscopic residual tumors, which, as reported in the literature, decreases significantly. This is quite concerning and could be attributed, among other factors, to challenges in performing adequate brachytherapy in this subgroup of patients, as reported by Verma *et al.* (<u>11</u>).

When analyzing the mortality found in this report compared to other studies consulted, it is important to underline that our institution serves as a referral center for radiotherapy treatment. As a result, all patients received radiotherapy, whereas, in the other studies, not all hysterectomized patients underwent radiotherapy.

The most important limitation of this study consists of being conducted at a single center, which, despite being a reference oncology center, does not represent the entirety of patients with this disease or the reality of treatment access that patients face in other oncology care centers in the country (20). Therefore, a prospective multicenter study would be desirable to characterize the real impact of inadequate hysterectomies in Ecuador.

Conclusions

The delayed diagnosis of cervical carcinoma and its inadequate staging amplify the likelihood of an inappropriate therapeutic approach, thereby notably affecting patient survival. This study calls attention to a substantial concern in Ecuador, shedding light on the prevalence of an inadequate initial therapeutic strategy, whose impact on overall survival is considerable. It is worth analyzing this situation in other institutions that manage oncological patients within the territory and in other low –and middle– income countries. For this reason, this analysis aimed to assess the impact of this problem and establish strategies for reducing inadequate hysterectomies.

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