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RESEARCH ARTICLE

Clinical and Histopathological Comparison of Two Historical Series of 142 Wertheim-Meigs Operations Performed in a Reference Center in Brazil

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Abstract

Introduction: Cervical cancer is the third-leading cause of death from cancer in Brazilian female population. Treatment depends on the clinical stage of the disease according to the classification of the International Federation of Gynecology and Obstetrics (FIGO). Radical hysterectomy with pelvic lymphadenectomy, the "Wertheim-Meigs" surgery, is a key intervention for tumors restricted to the cervix.

Methods: This retrospective study aimed to compare clinical and pathologic data on two historical series (2001-2007 and 2011-2014) of 142 patients submitted to Wertheim-Meigs surgery. The medical records were reviewed with special emphasis on clinical findings and pathological features.

Results: The clinical profile of these patients, such as age (average age of 48), parity (average of 4 children), and smoking (21% of patients were smokers) remained similar. Regarding pathological data, there was an increasing prevalence of adenocarcinoma compared to squamous cell carcinoma. In the two series presented and excluding other rare histologies, the percentage of CEC fell from 87.3% to 71.4% (p = 0.045). Pelvic lymph node metastasis raised from 7.2% to 20.3% on the latest series (p = 0.040). Histological grade and stromal invasion remained stable in both series. Other variables as average tumor size (> 2 cm or > 4 cm) and lymphovascular invasion showed small differences between the two groups evaluated, without statistical significance.

Conclusion: Was observed an increase of adenocarcinomas and positive pelvic lymph nodes in the comparison of the two historical series. Although lymphovascular invasion, tumor size and deep stromal invasion are also important prognostic indicators, it did not show significant growth. We present an introduction to this subject of how two historical series of the same service are substantially different in terms of variables, approached in such a short time difference of only four years between them.

Keywords

Uterine cervical neoplasms, Gynecologic surgical procedures, Adenocarcinoma, Carcinoma squamous cell

Introduction

Cervical cancer is the third-leading cause of death from cancer in Brazilian female population. For the year 2016, in Brazil, 16,340 new cases of cervical cancer are expected, with an estimated risk of 15.85 cases per 100,000 women. In the period from 2005 to 2009, overall survival was around 61% [1,2]. Human Papilloma Virus (HPV) is the most important etiologic factor in majority of cases of cervical cancer, with HPV DNA identified in approximately 95% of malignant cervical

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lesions. Other risk factors such as low socio-economic status, tobacco smoking, sexual habits, HIV, other sexually transmitted diseases, long-term oral contraceptive use, certain micronutrient deficiencies and genetic susceptibility have been suggested as determinants [3]. Treatment depends on the clinical stage of the disease according to the classification of the International Federation of Gynecology and Obstetrics (FIGO) [4,5].

Brazil still needs appropriate studies to assess the behavior and profile of this disease in our population. The surgical oncology service at Hospital Pérola Byington women's health reference center is reference for treatment of pelvic gynecologic malignancies in the State of São Paulo. In 2015, the women's health reference center performed 556 oncological procedures of the genital tract ranging from low-complexity surgery to high-complexity surgery. Of these surgeries performed, nearly 30% are related to cervical cancer or intraepithelial lesions. Almost 3/5 of the diagnosed cases are locally advanced and treated with chemoradiotherapy. Considering 112 cases of invasive cervical cancer that underwent surgery of any kind, including cone biopsy or physical examination under narcosis, only 26% were eligible for radical hysterectomy (Querleu-Morrow type C) [6].

Radical hysterectomy with pelvic lymph adenectomy, the "Wertheim-Meigs" surgery, is a key intervention for tumors restricted to the cervix or contiguous to upper vagina. The procedure is mainly indicated in the following conditions: microscopic tumor larger than 7 mm in length or 3 mm in stromal depth and macroscopic tumors less than 4 cm in diameter (stage IA2, IB1 and IIA1). According to the NCCN, this surgery could also be indicated in stages IB2, although the most usual approach is to use radiotherapy with concurrent chemotherapy in such cases [4,7]. Alternatively, ESMO suggest neoadjuvant chemotherapy followed by radical hysterectomy in selected cases, although it is not a standard practice [8].

In the final data of an anatomopathological examination, such as histologic type, tumor size, lymphovascular invasion, histological grade, stromal invasion, and lymph node status, all of them are prognostic and critical factors to define the adjuvant therapy [4,9]. A randomized trial of surgery versus radiotherapy for patients with stage IB1 to stage IIA cervical cancer demonstrated no difference in survival. The patients in this trial did not receive chemotherapy, and 84% of patients in the surgical arm with tumors measuring > 4 cm required postoperative radiotherapy. Morbidity was noted to be greater in patients who received both modalities, and therefore current recommendations are to try to use a single modality [10].

Methods

This study aimed to compare clinical and pathologic data on two historical series (2001-2007 and 2011-2014) of patients submitted to radical hysterectomy with pelvic lymph adenectomy (Wertheim-Meigs surgery). There was performed a retrospective review of 142 patients with clinical FIGO stage IA2-IIA1 cervical cancer, who were treated by surgery in our service between 2001-2007 (83 cases) and between 2011-2014 (59 cases). Data were retrieved from the hospital registry.

The medical records of these patients were reviewed with special emphasis on clinical findings such as patient age, smoking and parity, and pathological features. The tumors were classified according to cell type as follows: squamous cell carcinoma, adenocarcinoma and other unusual types, pathologic grade of well, moderately or poorly differentiated, greatest diameter of the primary tumor (larger than 2 or 4 cm); lymphovascular invasion; deep stromal invasion (more than 1/3 of cervical thickness) and pelvic lymph node metastasis. Descriptive analysis was used for categorical variables, such as frequencies and percentages, in the two different series. Statistical analysis was performed using the chi-square test when applicable, at a significance level of 5% (p-value ≤ 0.05).

Results

We have observed, in this study, that the clinical profile of patients operated from 2001 to 2007, and from 2011 to 2014 remained similar for the following risk factors: age (average age of 48), parity (average of 4 children), and smoking (21% of patients were smokers) (Table 1). Regarding pathological data, we see an increasing prevalence of adenocarcinoma (endocervical adenocarcinoma, mucinous adenocarcinoma, and adenosquamous) compared to Squamous Cell Carcinoma (SCC). In the two series presented and excluding other rare histologies, the percentage of CEC fell from 87.3% to 71.4% (p = 0.045). In turn, pelvic lymph node metastasis raised from 7.2% to 20.3% on the latest series (p

Table 1: Clinical information.

Clinical variable evaluated	Series 2001-2007 (n = 83)	Series 2011-2014 (n = 59)
Age (average)	45.9 (23-70 y)	48 (22-81 y)
Smoking		
Yes	16 (19.2%)	15 (25.4%)
No	15 (18%)	34 (57.6%)
Unknown	52 (62.8%)	10 (17%)
Parity (average)	4.6	3.9

Table 2: Histopathological variables.

Variables	Series 2001-2007	Series 2011-2014	P-value
SCC/ADENOCA			
SCC	69 (87.3)	35 (71.4)	0.045
ADENOCA	10 (12.7)	14 (28.6)	
Total	79 (100)	49 (100)	
SCC/ADENOCA			
SCC	69 (83.1)	35 (59.3)	0.005
ADENOCA	10 (12)	14 (23.7)	
Others	4 (4.8)	10 (16.9)	
Total	83 (100)	59 (100)	
Grade			
G1	9 (10.8)	11 (18.6)	0.051
G2	61 (73.5)	35 (59.3)	
G3	13 (15.7)	10 (16.9)	
NA	0 (0)	3 (5.1)	
Total	83 (100)	59 (100)	
LN			
LN +	6 (7.2)	12 (20.3)	0.040
LN -	77 (92.8)	47 (79.7)	
Total	83 (100)	59 (100)	
LVI			
LVI +	13 (15.7)	15 (25.4)	0.220
LVI -	70 (84.3)	44 (74.6)	
Total	83 (100)	59 (100)	
Size			
> 2 cm	29 (34.9)	30 (50.8)	0.085
≤ 2 cm	54 (65.1)	29 (49.2)	
Total	83 (100)	59 (100)	
Size			
> 4 cm	4 (4.8)	9 (15.3)	0.067
≤ 4 cm	79 (95.2)	50 (84.7)	
Total	83 (100)	59 (100)	
Stromal invasion			
> 1/3	37 (44.6)	25 (42.4)	0.929
≤ 1/3	46 (55.4)	34 (57.6)	
Total	83 (100)	59 (100)	

= 0.040). Histological grade and stromal invasion remained stable in both series. Other variables as average tumor size (> 2 cm or > 4 cm) and lymphovascular invasion showed small differences between the two groups evaluated, without statistical significance (Table 2 and Figure 1).

Discussion

HPV 16/18 account for two-thirds of cervical carcinomas in all continents. Persistent infection will result in the development of the premalignant Cervical Intraepithelial Neoplasia (CIN) or adenocarcinoma in situ. Various factors increase the development of persistent transformation, including cigarette smoking, long-term oral contraceptive use, high parity and co-infection with type 2 herpes simplex virus and the human immunodeficiency virus. Without treatment, the transition from dysplasia to invasive carcinoma may take years to decades to develop in most women. In addition, adenocarcinoma in situ appears to be more difficult to detect on Papanicolaou testing and this is thought to be one of the reasons for the increasing incidence of subtype of cervical cancer (HPV 18) [8,11]. The screening is realized through cytology each 3 years and with HPV and cytology co-testing every 5 years, preferred [7]. This combination demonstrated a slight increase in sensitivity for detection of CIN 2/3 (pre malign lesions). One limitation of the use of HPV testing in brazilian public medical service is the increased cost [2,12].

Studies have shown that over the past three decades, SCC of the cervix has been progressively decreasing in proportion to the increase of adenocarcinoma, also found in our study [13-17]. However, in a more current reality, this can be explained due to the better public access to the examination of cervical cytological screen-

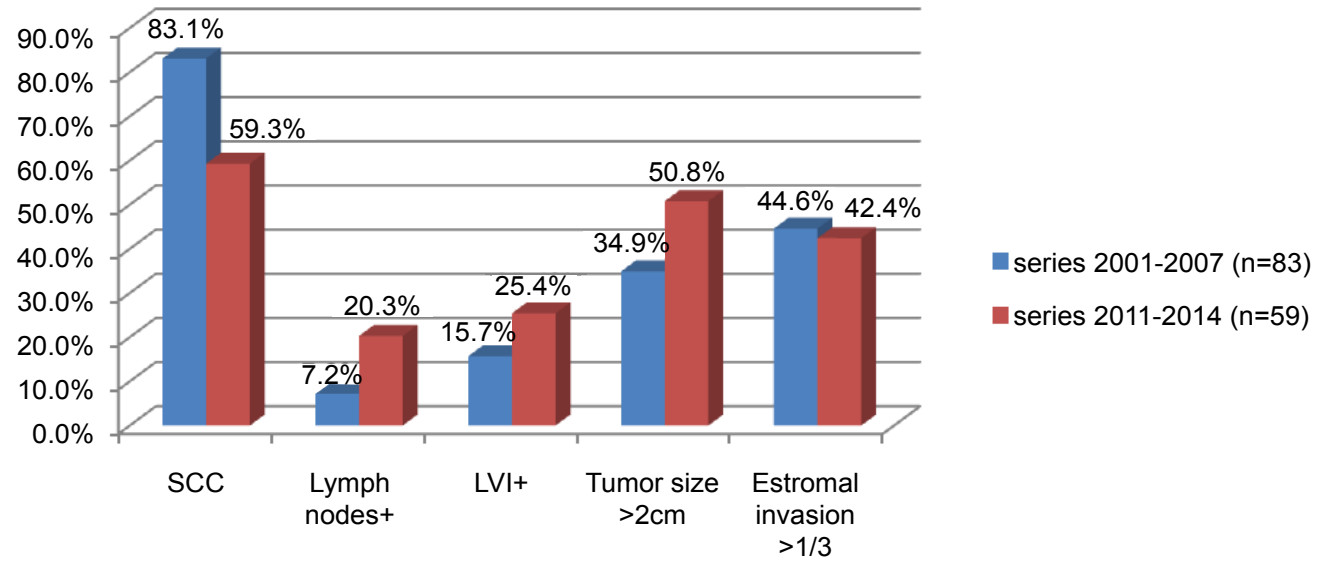

Figure 1: Squamous cell carcinoma. Lymph node metastasis, Lymphovascular Invasion (LVI), tumor size > 2 cm and stromal invasion > 1/3.

SCC (p = 0.045); lymph nodes + (p = 0.04); lymphovascular invasion, tumor diameter > 2 cm, estromal invasion: p > 0.05.

ing. This examination has better effectiveness in identifying intraepithelial neoplasias and precursors of SCC in relation to precursors of adenocarcinomas. Positive pelvic lymph node is one of the most important prognostic factors in cervical cancer [4,7-9,13,18,19]. Increased rates of lymph node metastasis in the comparison of the two historical series maintained a close relationship with the concomitant growth of adenocarcinoma type. On the other hand, although was observed an increase of adenocarcinomas and positive pelvic lymph nodes in the comparison of the two historical series. Although lymphovascular invasion, tumor size and deep stromal invasion are also important prognostic indicators, it did not show significant growth.

In this context, a possible explanation to recommend a radical hysterectomy for cancers with poor prognostic factors and/or advanced locally is the limitation of tests recommended by the International Federation of Gynecology and Obstetrics (FIGO), which essentially recommends the completion of a thorough physical examination, associated with a minimum of subsidiary propedeutics, such as evaluation of the urinary tract, concerning the clinical staging of the disease. But, even imaging tests such as MRI and incisional biopsies may not give a proper assessment of stromal invasion, lymph node enlargement, invasion of isthmus and body of the uterus, which would contraindicate the surgical procedure when associated. Another reason may be the development and growth of surgical teams in the period surveyed towards a more aggressive approach against tumors of poorer prognosis. However, we have to assess whether this radicalism has reflected in better oncologic results with acceptable toxicity to the patient. This study is already underway.

Conclusion

Clearly, much remains to be known about the biological behavior, as well as the clinical and epidemiological profile of cervical cancer in Brazil. The study is only an introduction to this subject and of how two historical series of the same service are substantially different in terms of variables approached in such a short time (difference of only four years between series). Thus, we should not treat cervical cancer as a static condition, quite the contrary, it is full of variations, which depend on the population and the period studied.

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