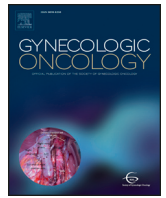




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## Is parametrectomy always necessary in early-stage cervical cancer?

Glauco Baiocchi<sup>a,\*</sup>, Louise de Brot<sup>b</sup>, Carlos Chaves Faloppa<sup>a</sup>, Henrique Mantoan<sup>a</sup>, Matheus Rodrigues Duque<sup>a</sup>,  
Levon Badiglian-Filho<sup>a</sup>, Alexandre Andre Balieiro Anastacio da Costa<sup>c</sup>, Lillian Yuri Kumagai<sup>a</sup>

<sup>a</sup> Department of Gynecologic Oncology, AC Camargo Cancer Center, Sao Paulo, Brazil

<sup>b</sup> Department of Anatomic Pathology, AC Camargo Cancer Center, Sao Paulo, Brazil

<sup>c</sup> Department of Medical Oncology, AC Camargo Cancer Center, Sao Paulo, Brazil

## HIGHLIGHTS

- Patients with early-stage cervical cancer may have a low risk of parametrial invasion (PI).
- The presence of LVSI and lymph node metastasis correlates independently with PI.
- Patients with tumors  $\leq 2$  cm and those who lack LVSI are unlikely to have PI.

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## ABSTRACT

**Objective.** Increasing data suggest that patients with early-stage cervical cancer and favorable pathological characteristics have a low risk of parametrial invasion (PI) and benefit from less radical surgery. Our aim was to evaluate the clinical-pathological factors that are related to PI and identify a group of patients who are at low risk for PI.

**Methods.** We analyzed a series of 345 patients with stage Ia2 to Ib2 cervical cancer, for which they underwent radical surgery from January 1990 to October 2016 at AC Camargo Cancer Center. Chi-square and Fisher's exact tests were used to analyze the correlations between PI and clinicopathological variables.

**Results.** A total of 217 (62.9%) patients were classified as having squamous cell carcinoma, and 128 (37.1%) had adenocarcinoma or adenosquamous carcinoma. Sixteen (4.6%) patients had PI. The presence of perineural invasion ( $p = 0.003$ ), tumor size  $> 2$  cm ( $p = 0.044$ ), depth of invasion  $> 10$  mm ( $p = 0.004$ ), the presence of lymphovascular space invasion (LVSI) ( $p < 0.001$ ), and lymph node metastasis ( $p < 0.001$ ) were related to PI. However, only LVSI ( $p = 0.043$ ) and lymph node metastasis ( $p < 0.001$ ) remained risk factors for PI in the multivariate analysis. Of the patients with tumors  $\leq 2$  cm and no LVSI, only 1 (1.2%) had PI; however, this patient had lymph node metastasis and deep stromal invasion ( $> 10$  mm). No patient with tumor size  $\leq 2$  cm and negative lymph nodes had PI.

**Conclusions.** Patients with tumors  $\leq 2$  cm and those who lack LVSI are unlikely to have PI, unless lymph node metastasis or deep stromal invasion is present. Our data can help select patients in whom a more conservative approach is warranted, such as simple hysterectomy and simple trachelectomy that is associated with pelvic lymphadenectomy.

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## 1. Introduction

Cervical cancer is the third most common malignant neoplasm in women worldwide and the fourth leading cause of mortality due to cancer. Every year, nearly 530,000 cases of cervical cancer are diagnosed, resulting in over 260,000 deaths [1]. The current standard treatment

for early-stage cervical cancer (stages Ia2–Ib1) is radical hysterectomy with pelvic lymphadenectomy. However, for select patients who still wish to preserve their fertility, radical trachelectomy with pelvic lymphadenectomy is a feasible and safe alternative, with similar results with regard to recurrence and survival [2–5]. These data raised the possibility that less radical procedures can be offered to other patients who do not plan to have children.

Radical hysterectomy entails partial resection of the parametrium; consequently, there are several morbidities that are related to lesioning of the autonomic plexus, such as bladder dysfunction, sexual dysfunction (vaginal dryness), and rectal dysmotility [6]. Theoretically, the

\* Corresponding author at: Departamento de Ginecologia Oncológica, AC Camargo Cancer Center, Rua Antonio Prudente, 211, 01509-010 São Paulo, Brazil.

E-mail addresses: [glbaiocchi@yahoo.com.br](mailto:glbaiocchi@yahoo.com.br), [glauco.baiocchi@accamargo.org.br](mailto:glauco.baiocchi@accamargo.org.br) (G. Baiocchi).

autonomic plexus can be preserved during surgery by 2 means. First, parametrial resection is performed, and radicality is maintained using nerve-sparing techniques; this approach requires specific training and is less reproducible. Alternatively, less radical surgeries can be offered, with parametrial and paracervical preservation.

Several retrospective studies have concluded that there is a low risk of parametrial dissemination in early cervical cancer with favorable pathological variables, reporting a risk of parametrial invasion (PI) of <1%. This finding supports that parametrial resection can be spared during surgical treatment. However, no study reported patients treated in a low-middle income country.

Our aim was to evaluate the pathological risk variables for PI in cases of early-stage cervical cancer who have been subjected to radical surgery and recommend a subgroup that can forgo parametrectomy.

## 2. Methods

We analyzed a series of 487 patients with stage Ia2 to IIa1 cervical cancer, for which surgical treatment was performed from January 1990 to October 2016 at AC Camargo Cancer Center. We excluded stage IIa1 patients and those without a description of parametrial status in their pathological records; ultimately, 345 patients were evaluated as a case-control study where the interest outcome was parametrial invasion. All patients had stage Ia2 to Ib2 disease and received surgical treatment, including radical hysterectomy and radical trachelectomy with pelvic lymph node dissection.

A database was constructed using SPSS, version 20.0 for Mac (SPSS, Inc., Chicago, IL). Chi-square and Fisher's exact tests were used to analyze the correlations between categories and clinicopathological variables. For all tests,  $p < 0.05$  was considered to be significant.

## 3. Results

The median age was 45 years (range, 23–80). A total of 13 (3.8%), 273 (79.1%), and 59 (17.1%) patients were classified as having stage Ia2, Ib1, and Ib2 disease, respectively. Twelve (3.4%) patients had fertility-sparing radical trachelectomy. Further, 217 cases (62.9%) were squamous cell carcinomas, and 128 (37.1%) were adenocarcinomas or adenosquamous carcinomas. The median number of dissected lymph nodes was 25 (range, 4–91), and 52 (15.1%) patients had lymph node metastasis. Sixteen (4.6%) subjects had PI. Two (2/16) patients were considered as having PI due to the presence of parametrial positive nodes versus 14 after direct microscopic extension. The clinical and pathological variables are summarized in Table 1.

Only 1.3% of patients who lacked LVSI had PI, compared with 12.6% of patients with LVSI ( $p < 0.001$ ). When lymph nodes were positive, 21.2% of patients had PI, versus 1.7% when they were negative ( $p < 0.001$ ). Further, 68.7% and 81.2% of patients with PI had lymph node metastasis and LVSI, respectively. The presence of perineural invasion ( $p = 0.003$ ), tumor size  $> 2$  cm ( $p = 0.044$ ), and depth of invasion  $> 10$  mm ( $p = 0.004$ ) were the other variables that were related to PI. Tumor size and depth of invasion also correlated with PI when analyzed as continuous variables (Table 2).

Of the 16 patients with PI, 5 did not have node metastasis; however, all 5 patients had LVSI. Moreover, only 2 patients with tumors  $\leq 2$  cm had PI, both of whom had node metastasis and depth of invasion  $> 10$  mm. No patient with tumors  $\leq 2$  cm and negative lymph nodes had PI. The cases with PI are summarized in Table 3.

A total of 20 (21.6%) of 102 patients with tumors  $\leq 2$  cm had LVSI, 6 (30%) of whom had lymph node metastasis and 1 (16.7%) of whom had PI. Two of 102 (1.9%) patients with tumors  $\leq 2$  cm had PI and also had lymph node metastasis. Conversely, 64 (35.1%) of 182 patients with tumors  $> 2$  cm had LVSI; of these subjects, 18 (28.1%) had lymph node metastasis and 7 (38.9%) had PI. Overall, 14 of 182 (7.7%) patients with tumors  $> 2$  cm had PI. Moreover, any patient who lacked LVSI and had

**Table 1**

Clinical and pathological characteristics of the 345 patients with stages Ia2–Ib2 cervical cancer submitted to radical surgery. (AC Camargo Cancer Center 1990–2016).

Variable		No. of patients	(%)
Stage (FIGO)	Ia2	13	3.8
	Ib1	273	79.1
	Ib2	59	17.1
Type of surgery	Type B RH <sup>a</sup>	16	4.6
	Type C1 RH <sup>a</sup>	78	22.4
	Type C2 RH <sup>a</sup>	242	69.5
	Radical trachelectomy	12	3.4
Histologic type	Squamous cell	217	62.9
	Adenocarcinoma	115	33.3
Histologic grade	Adenosquamous	13	3.8
	Grade 1	52	16.4
	Grade 2	195	61.3
	Grade 3	71	22.3
LVSI <sup>b</sup>	Missing data	27	7.8
	No	228	68.9
	Yes	103	31.1
Perineural invasion	Missing data	14	4.1
	No	266	82.1
	Yes	58	17.9
Sentinel node protocol	Missing data	21	6.1
	No	290	84.1
	Yes	55	15.9
Lymph node metastasis	No	293	84.9
	Yes	52	15.1
Parametrial invasion	No	329	95.4
	Yes	16	4.6
Tumor size	$\leq 2$ cm	107	36
	$> 2$ and $\leq 4$ cm	131	44.1
	$> 4$ cm	59	19.9
	Missing data	48	13.9
Depth of invasion	$\leq 10$ mm	185	64.5
	$> 10$ mm	102	35.5
	Missing data	58	16.8

<sup>a</sup> RH: Radical hysterectomy.

<sup>b</sup> LVSI: Lymphovascular space invasion.

negative lymph node metastasis developed PI, regardless of tumor size (Fig. 1).

## 4. Discussion

In 1995, Kinney et al. [7] analyzed 387 patients with squamous cell cervical cancer, of whom 21.4% had favorable pathological features,

**Table 2**

Association between clinical-pathological variables and the presence of parametrial invasion for 345 patients with stages Ia2–Ib2 cervical cancer submitted to radical surgery. (AC Camargo Cancer Center 1990–2016).

Variable	Category	Parametrial invasion		
		Absent	Present	p
Age	Continuous			0.60
Tumor size	Continuous			0.036
Depth of invasion	Continuous			0.005
Histological type	Squamous cell	208	9 (4.1%)	0.57
	Adenocarcinoma <sup>a</sup>	121	7 (5.5%)	
Tumor size	$\leq 2$ cm	105	2 (1.9%)	0.044
	$> 2$ cm	176	14 (7.4%)	
Lymph node metastasis	No	288	5 (1.7%)	$< 0.001$
	Yes	41	11 (21.2%)	
Histological grade	Grades 1 and 2	233	14 (5.7%)	0.53
	Grade 3	69	2 (2.8%)	
Depth of stromal invasion	$\leq 10$ mm	180	5 (2.7%)	0.004
	$> 10$ mm	91	11 (10.8%)	
LVSI <sup>b</sup>	No	225	3 (1.3%)	$< 0.001$
	Yes	90	13 (12.6%)	
Perineural invasion	No	258	8 (3.0%)	0.003
	Yes	50	8 (13.8%)	

<sup>a</sup> Includes adenocarcinoma and adenosquamous carcinoma.

<sup>b</sup> LVSI: Lymphovascular space invasion.

**Table 3**  
Clinical and pathological characteristics of the 16 patients with parametrial invasion.

Case	Age (y)	Stage	Histology	Grade	LVSI <sup>a</sup>	Perineural invasion	Tumor size (cm)	Depth of invasion (mm)	LNM <sup>b</sup>
1.	66	IB2	SCC <sup>c</sup>	G2	No	No	5.0	25	Yes
2.	44	IB1	SCC	G2	Yes	Yes	3.5	25	Yes
3.	39	IB1	SCC	G2	Yes	Yes	4.0	16	No
4.	60	IB1	SCC	G2	Yes	No	3.5	20	Yes
5.	33	IB2	SCC	G2	Yes	Yes	4.2	16	Yes
6.	33	IB1	SCC	G2	No	Yes	2.0	15	Yes
7.	39	IB1	SCC	G2	Yes	Yes	3.0	>10	Yes <sup>f</sup>
8.	32	IB1	SCC	G2	Yes	No	3.5	2.8	Yes <sup>f</sup>
9.	45	IB1	SCC	G2	Yes	No	3.0	8	No
10.	52	IB1	AC <sup>d</sup>	G2	Yes	No	3.7	12	No
11.	56	IB1	AC	G3	Yes	Yes	2.0	12	Yes
12.	62	IB2	AC	G2	Yes	Yes	4.5	11	No
13.	61	IB2	AC	G2	Yes	Yes	5.5	15	No
14.	34	IB1	AC	G2	No	No	2.5	10	Yes
15.	44	IB2	AS <sup>e</sup>	G3	Yes	No	5.5	7	Yes
16.	58	IB2	AS	G2	Yes	No	4.5	10	Yes

<sup>a</sup> LVSI: Lymphovascular space invasion.

<sup>b</sup> LNM: Lymph node metastasis.

<sup>c</sup> SCC: Squamous cell carcinoma.

<sup>d</sup> AC: Adenocarcinoma.

<sup>e</sup> AS: Adenosquamous carcinoma.

<sup>f</sup> Cases with parametrial and pelvic lymph node metastasis.

including tumor size  $\leq 2$  cm and absence of LVSI—no patient had PI. Subsequently, Covens et al. [8] noted PI in 4% of 842 patients. The risk factors for PI were age, presence of LVSI, grade 2 and 3 tumors, depth of stromal invasion, and presence of lymph node metastasis. The prevalence of PI in patients with negative nodes, tumors  $\leq 2$  cm, and stromal invasion  $\leq 10$  mm was 0.6%.

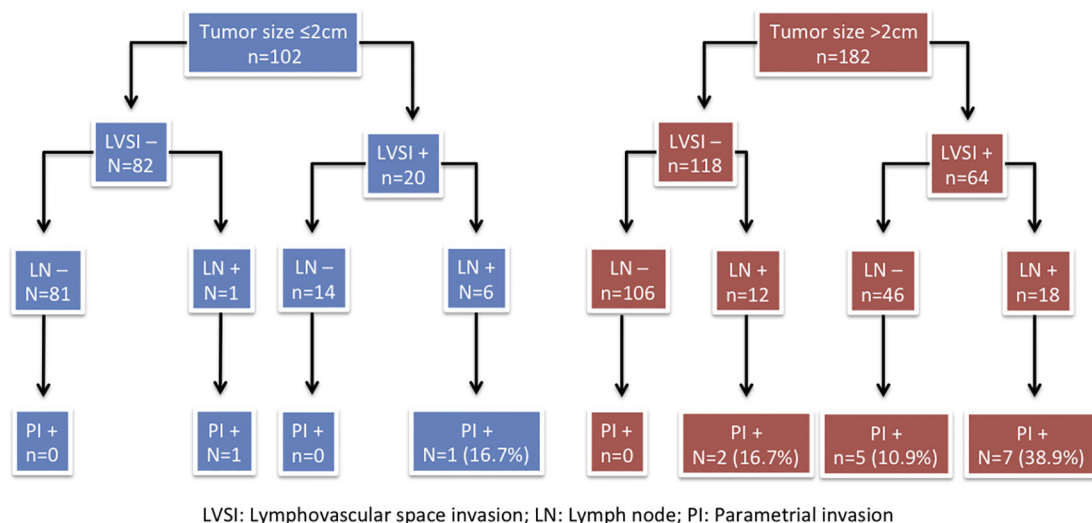
Similarly, Wright et al. [9] suggested several risk factors for PI. Of 594 patients, 64 (10.8%) had PI, and the risk of PI was 0.4% for patients with negative nodes, tumors  $\leq 2$  cm, and no LVSI. Stegeman et al. [10] evaluated 103 patients with tumors  $< 2$  cm, stromal invasion  $< 10$  mm, and negative lymph nodes. Two patients (1.9%) developed PI, but both of them had LVSI.

Frumovitz et al. [11] recorded PI in 7.7% of 350 patients. No patient ( $n = 125$ ) without LVSI and harboring tumors  $\leq 2$  cm had PI. In contrast to their findings, we observed PI in 1 patient with tumors  $\leq 2$  cm and no LVSI. However, this case had lymph node metastasis and deep stromal invasion ( $> 10$  mm), highlighting the significance of other risk factors for PI.

In the study at MD Anderson Cancer Center [11], PI was linked to lymph node metastasis. However, 44% (12/27) of patients with PI had

negative lymph nodes. In our series, 31.2% (5/16) of women with PI did not have lymph node metastasis. Notably, these 5 cases had tumors  $> 2$  cm and LVSI. No patient with tumors  $\leq 2$  cm and lacking node metastasis had PI, and this characteristics comprises 30.3% of our cases. Theoretically, had we performed parametrectomy in all tumors  $\leq 2$  cm, the risk of leaving a positive parametrium would have been 1.9%. However, all patients with tumors  $\leq 2$  cm and PI ( $n = 2$ ) also had lymph node metastasis.

Negative lymph nodes have been suggested as an inclusion criterion for less radical surgery [8–10]. Although node status is not known at the time of less radical surgeries, if PI is found in patients with small tumors ( $\leq 2$  cm) only when positive node are present, patients with parametrial involvement should undergo adjuvant pelvic chemoradiotherapy, thus treating the positive spared parametrium. Our patients with small tumors and PI also had lymph node metastasis, warranting additional adjuvant chemoradiotherapy. Moreover, the absence of LVSI and deep stromal invasion ( $> 10$  mm) could be used to select patients with small tumors ( $\leq 2$  cm) after primary conization who can forgo parametrectomy. In our data, no patient with tumors  $\leq 2$  cm and the absence of LVSI and deep stromal invasion had parametrial involvement.



**Fig. 1.** Schematic description of patients regarding tumor size, presence of lymphovascular space invasion, lymph node metastasis and parametrial invasion.

Four prospective clinical trials are evaluating a conservative approach in patients with low-risk, early-stage cervical cancer. The ConCerv trial, led by Schmeler and et al., is determining the safety and feasibility of conservative surgery [6]. ConCerv is a multi-institutional international trial with a desired sample size of 100 patients that includes those with tumor size  $\leq 2$  cm, squamous cell carcinoma (any grade) or adenocarcinoma (grade 1 or 2), and absence of LVSI. Patients will undergo simple hysterectomy or conization with pelvic node dissection and sentinel mapping.

The Gynecologic Cancer Intergroup trial (SHAPE Trial), led by Plante and colleagues [NCT01658930], is a randomized trial that is comparing radical hysterectomy and pelvic node dissection with simple hysterectomy and pelvic node dissection. The inclusion criteria are tumor size  $< 2$  cm, squamous cell carcinoma or adenocarcinoma, and  $< 10$  mm stromal invasion after conization or  $< 50\%$  stromal invasion on magnetic resonance imaging. All tumor grades and LVSI are allowed. The primary objectives are to determine whether simple hysterectomy in patients with low-risk cervical cancer is safe and associated with less morbidity and whether overall survival is similar between study groups. The total anticipated accrual is 700 patients.

The primary objectives of GOG 278 [NCT01649089] are to examine the morbidity of nonradical surgery with regard to bladder, bowel, and sexual function and determine the incidence and severity of lymphedema. The eligibility criteria are squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma; tumor size  $\leq 2$  cm, any grade; and depth of invasion  $\leq 10$  mm. All patients should have had a previous conization with negative margins. The sample size is anticipated to be 200 patients.

Finally, the LESSER trial is being planned by Brazilian institutions [NCT02613286]. This study is an open-label, multicenter, randomized, phase II noninferiority trial (proof-of-concept study) that will evaluate the safety of simple hysterectomy and pelvic lymph node dissection compared with the standard modified radical hysterectomy in patients with stage IA2-IB1 cervical cancer (tumor size  $\leq 2$  cm). The primary outcome is progression-free survival at 3 years, and secondary outcomes include treatment-related adverse effects and patient-reported quality of life.

Although important retrospective studies have addressed the risk factors for parametrial invasion, our study is the first from a low-middle income country where almost 85% of cervical cancers are found. Additionally, a great number of women with cervical cancer, which live in low-middle income countries where surgical resources are usually scarce, may benefit from less radical surgeries without compromising their outcome.

Overall, our series is comparable in size with most of the significant studies on less radical surgery in cervical cancer and contributes

valuable data. Moreover, our findings can help stratify patients with regard to the risk of parametrial invasion. Unfortunately, it suffers from the inherent biases of a retrospective, single-institution study design.

In conclusion, our data corroborate current findings—that the risk of PI is  $< 1\%$  for early-stage patients with low-risk pathological features. This subset of patients can be identified by combining tumor size  $\leq 2$  cm with: 1) the absence of LVSI and deep stromal invasion or 2) negative pelvic lymph nodes regardless of LVSI status. Notably, we also did not find PI in patients with tumor  $> 2$  cm but who had both negative lymph node and absence of LVSI. However, conservative surgery for patients with early-stage cervical cancer remains an approach that should be considered only in the setting of clinical trials.

#### Conflict of interest statement

The authors declare no conflict of interest.

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