

Review

Minimizing Fertility-sparing Treatment for Low Volume Early Stage Cervical Cancer; Is Less the (R)Evolution?

CHARALAMPOS THEOFANAKIS¹, DIMITRIOS HAIDOPOULOS¹, NIKOLAOS THOMAKOS¹,
ALEXANDROS RODOLAKIS¹ and CHRISTINA FOTOPOULOU²

¹Unit of Gynecologic Oncology, 1st Department of Obstetrics & Gynecology,
Alexandra Hospital, National and Kapodistrian University of Athens, Athens, Greece;

²Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, U.K.

Abstract. *Background/Aim:* The aim of this study was to conduct a review on less radical fertility-sparing surgical treatment for early-stage cervical cancer. *Materials and Methods:* We conducted a Medline search from 2014 to 2018 regarding less radical fertility-sparing techniques, such as simple trachelectomy or cervical conization, with pelvic lymphadenectomy. We also assessed the impact of the removal of the parametrium on the obstetric and oncologic outcome, in women who desire to preserve their fertility. *Results:* We analyzed studies about cervical conization and simple trachelectomy, together with pelvic lymphadenectomy in early-stage cervical cancer. We also assessed the importance of parametrial involvement in reducing morbidity, without jeopardizing the oncologic outcome of these patients. Studies demonstrate that in tumors ≤ 2 cm, without lymphovascular Space Invasion and without evidence of parametrial involvement, a less radical fertility-sparing surgical approach could increase pregnancy rates and have a positive effect on the quality of life of these patients. *Conclusion:* Standard fertility-sparing treatment for early-stage cervical cancer is still radical trachelectomy with pelvic lymphadenectomy. However, studies suggest that the omission of parametrectomy is a feasible and safe option. Simple trachelectomy or cervical conization, both combined with pelvic lymphadenectomy are acceptable approaches in a selected group of patients with early-stage cervical cancer.

Cervical cancer represents the fourth most common malignancy in women, with over half a million new cases each year worldwide (1, 2). Cervical cancer appears between 30 and 40 years of age, and is attributed to the exposure of the affected women to the Human Papilloma virus and the long latency in the natural history of the infection (3). This implies that a large majority of newly diagnosed cervical cancer affects young women with childbearing potential who wish to preserve their fertility, after completion of their oncologic treatment. Due to improved, well established HPV-based screening programs and liquid-based cytology, but also higher public awareness, we have nowadays, more than ever before, the capacity of diagnosing the disease in still early stages and follow potentially less radical surgical options, which do not significantly compromise fertility (4).

The standard, non-fertility-sparing, surgical treatment for early, locally limited disease (5), as described by the International Federation of Obstetrics & Gynecology (FIGO), is the radical hysterectomy with systematic pelvic lymphadenectomy. Through surgical advances such as nerve sparing dissection, sentinel lymph node techniques and centralization of care, surgical morbidity of radical cervical cancer surgery has been significantly reduced over the years. However, as any surgical approach, also radical hysterectomy harbors potential risks and carries morbidity, associated with short and long-term impact on patient's quality of life (6, 7). Moreover, due to the lack of randomized controlled trials, clinicians tend to tailor the extent of their surgical radicality in a rather arbitrary way, based on one's philosophy, experience and skills, since there is no well-established evidence of how radical is radical enough without compromising oncologic safety.

For women who wish a fertility sparing approach, radical trachelectomy is a viable and oncologically safe option for tumors less than 2 cm; nevertheless, even with this surgical technique, reproductive outcomes may be compromised due

Correspondence to: Theofanakis Charalampos, Michalakopoulou 88, 11528 Athens, Greece. Tel: +30 2107770921, +30 6973042478, e-mail: ch.theofanakis@gmail.com

Key Words: Cervical cancer, small volume, simple trachelectomy, conization, parametrial involvement, pelvic lymphadenectomy, review.

to a well described higher risk of prematurity, cervical stenosis and scar tissue formation and necessity of a caesarean section (8, 9).

Current universal trend leans towards a more minimalistic and fertility sparing treatment in young women with small volume and locally limited disease. Thus, many authors have suggested less radical surgical approaches. The goal is to reduce, not only the overall but especially the fertility affecting morbidity, derived from radical dissection. These approaches range from simple cone excision to simple trachelectomy, in combination with pelvic lymph node dissection or sentinel lymph node biopsy alone. The aim of the present review is to discuss the current evidence of the non-radical therapeutic approaches for early stage cervical cancer.

Materials and Methods

A literature search on PubMed from 2014 to 2018 was performed, to evaluate simple trachelectomy and conization as alternative fertility-sparing options to radical surgery for early stage cervical cancer. Earlier years before 2014 have been already covered by a review by Ramirez *et al.* (10). We used the following Medical Subject Headings (MeSH) terms: “early stage cervical cancer”, “simple trachelectomy”, “cervical conization”, “less radical surgery”, “squamous cell cervical carcinoma”, “cervical adenocarcinoma”, “adenosquamous cervical carcinoma”, “pelvic lymphadenectomy” and “lymph node dissection”. Search was limited to publications in English language. Additional literature was searched through cross-references of the articles retrieved. Articles that did not report on oncologic outcome and survival were not eligible and not included in this report. Regarding fertility sparing surgery, we only included articles that reported also on fertility outcome.

Results

We identified a total of 46 articles in the last 5 years regarding cervical conization [31] and simple trachelectomy [15] with pelvic lymphadenectomy for the treatment of early stage cervical cancer. Of those, 8 were eligible for the present analysis, since we chose to exclude case reports and review papers and also studies not published in the English language.

Conization and pelvic lymphadenectomy. We identified 31 articles regarding cervical conization for the treatment of early-stage cervical cancer in the last 5 years. Among them, 7 were systematic reviews, 4 were published in a non-English language and 15 articles were irrelevant to the subject. Overall, we present the findings of 5 retrospective studies that met our criteria (Table I).

Bouchard-Fortier *et al.*, assessed the oncological safety of omitting parametrectomy in a study of 51 patients with early-stage cervical cancer, who underwent simple hysterectomy or cone biopsy. The surgical approach was determined by the

need for fertility preservation, combined with assessment of the pelvic lymph nodes. Twenty-two patients were offered a simple hysterectomy, while 29 underwent a cone biopsy. Of those, 29 patients were offered systematic pelvic lymphadenectomy while 22 patients had sentinel lymph node biopsy only. The main histologic type was squamous cell carcinoma (51%), followed by adenocarcinoma (43%) and adenosquamous carcinoma (6%). Fifty-five percent of cases were FIGO stage IA1, 20% stage IA2 and 25.5% stage IB1 (28, 10 and 13 patients, respectively). Lymphovascular space invasion (LVSI) was present in 18 women (35%), while surgical margins were negative in all patients. Median follow-up was 21 months with no recurrences reported. There were no intraoperative or postoperative complications and the median blood loss was 100 ml. The authors concluded that a well-selected group of patients with favorable prognostic factors could be eligible for non-radical surgery for the treatment of early-stage cervical cancer (11).

In a recent retrospective study by Tomao *et al.*, the authors analyzed 54 patients with cervical cancer FIGO stage IA2 to IB1, 23 of which were entirely treated at the European Institute of Oncology (IEO), Milan, while the rest 31 patients were referred to IEO after the cone biopsy. Thirty-three patients (61.1%) presented with squamous cell carcinoma, 19 (35.2%) with adenocarcinoma and 2 (3.7%) with adenosquamous carcinoma, while LVSI was detected in 12 patients (22.2%). Treatment modality consisted of excisional cone and laparoscopic pelvic lymphadenectomy. Referred patients were only subjected to laparoscopic lymphadenectomy, while a second cone was performed when histopathologic review of the previous cone specimens revealed neoplastic invasion close (<3 mm) to or involving the section margins, postoperative positive Papanicolaou smears and/or cervical biopsy. The median follow-up period was 55 months (range=7-144 months) and the recurrence rate was 13%. Follow-up visits consisted of physical and pelvic examination, transvaginal sonography, Papanicolaou smear, HPV test, colposcopy and squamous cell carcinoma (SCC) serum marker assay. Two relapses were reported in the IA2 stage group and 5 in the IB1 stage groups, with a local cervical recurrence rate of 86% (6 of 7 cases). Five of these relapses were detected *via* Papanicolaou test (71%). One case of nodal relapse was recorded in a patient who had focal LVSI at the first conization. Because of inadequate free margins on the first specimen, the patient underwent a second conization at the time of lymphadenectomy. The final pathology report described a total of 31 negative pelvic lymph nodes. This case is noteworthy, since the patient conceived 4 months after the second conization and pelvic lymphadenectomy, which was against medical advice, and relapse occurred 14 months later, in the region of the right obturator. The patient received carboplatin and paclitaxel every week for 6 cycles. This case demonstrates the importance of delaying pregnancy for at least a year after treatment.

Table I. Simple conization and lymphadenectomy for early-stage cervical cancer.

Study	N	FIGO stage	Histology	LNDs removed	LVSI	Recurrences	Obstetrical outcome
Andikyan, 2013 (13)	10	IA1: 7 (LVSI+) IB1: 3	SCC: 8 Adenoca: 1 Clear cell: 1	SLN	7	0	3 (no further information)
Bouchard-Fortier, 2014 (11)	17	IA2:4 IB1:13	SCC: 12 Adenoca: 4 Glassy cell: 1	18	4	0	Term: 2 Miscarriages: 0
Lindsay, 2014 (14)	43	IA1: 2 IA2: 4 IB1: 37	SCC: 28 Adenoca: 11 Adenosq: 4	18.5	16	2	Term: 10 Preterm: 4 Miscarriage: 1 Termination: 1
Ditto, 2014 (15)	22	IA2: 6 IB1: 16	SCC: 10 Adenoca: 11 Adenosq: 1	26	9	2	Term: 4 Preterm: 1 Miscarriage: 1
Tomao, 2017 (12)	54	IA2:13 IB1: 41	SCC: 33 Adenoca: 19 Adenosq: 2	22.4	12	7	Term: 19 Miscarriages: 1

The overall survival was 100% within a median FU of 55 months (range=7-144 months) and the pregnancy rate, in total, was 80%. The authors concluded that this procedure could be an alternative option to simple or radical trachelectomy, but that to better define the recurrence rate related to this conservative approach, further multicenter studies are warranted. The importance of tertiary referral was emphasized and also the importance of Papanicolaou test in the follow-up of these patients after cone, due to the local patterns of recurrence (12).

The feasibility of a less radical approach to early stage cervical cancer was evaluated by Andikyan *et al.*, through a retrospective analysis of 10 patients, treated with cervical cone biopsy and sentinel lymph node biopsy, while pelvic lymphadenectomy was performed in cases of suspicious lymph nodes. Seven patients (70%) had stage IA1 disease with lymph vascular space invasion and 3 (30%) had microscopic IB1. Histology indicated that there were 8 (80%) patients with squamous cell carcinoma, 1 (10%) patient with adenocarcinoma and 1 (10%) patient with clear cell carcinoma of the cervix. All patients had a radiologic work-up preoperatively, which included an MRI and PET-CT, with negative findings. Because all patients were referred by other centers, in 9 out of 10, cervical conization was repeated, while the 10th patient underwent only cervical biopsies because of a previous large cone. No cerclage was placed. All patients underwent sentinel lymph node mapping with the use of blue dye, followed by selective pelvic lymphadenectomy of any suspicious lymph nodes and side-specific lymphadenectomy if 1 pelvic sidewall did not map. In 1 patient with invasive squamous cell carcinoma, a hysterectomy was performed by patient's choice, 3 months

after the cervical cone, even though she was counseled that a conservative approach was reasonable. None of the patients had residual invasive cervical carcinoma in the second cone specimen. The median number of sentinel lymph nodes examined was 4 (range=2-8) and were all negative for metastasis. With a median follow-up of 17 months (range=1-83 months), no recurrences were observed and 3 (30%) patients achieved spontaneous pregnancy. The authors stated that in selected patients with small-volume stage I cervical cancer, cervical conization and sentinel lymph node mapping is an acceptable treatment modality (13).

Lindsay *et al.*, presented a retrospective study of 43 patients with early stage cervical cancer, who underwent fertility preserving management with repeat large loop excision of the transformation zone (LLETZ) and laparoscopic bilateral pelvic lymphadenectomy (BPND). All patients had a history of LLETZ/punch biopsy, performed at their local colposcopy clinic for suspected high-grade cervical intraepithelial neoplasia. However, microscopic cervical cancers were diagnosed on pathological analysis; histopathology was reviewed by 2 expert pathologists and all cases were discussed in the multidisciplinary tumor board (MDT).

Histology reported 28 (65.1%) cases of squamous carcinoma, 11 (25.6%) of adenocarcinoma and 4 (9.3%) cases of adenosquamous carcinoma. Forty-two patients were offered a second LLETZ, 29 of which presented with no residual disease, while 8 had residual carcinoma and 5 had residual high-grade CIN or cervical glandular intraepithelial neoplasia. Three patients with residual carcinoma in the second LLETZ were offered a third LLETZ, which did not reveal any residual tumor or dysplasia. One patient had a

single LLETZ, with complete removal of the stage IA1 squamous cell cancer with LVSI and HGCIN.

Seven hundred ninety-five lymph nodes were retrieved from all 43 patients and the mean nodal count was 18.5 (median 18; range=5-46). Two positive nodes were retrieved from a single patient (1 from the right and 1 from the left side of the pelvis). Mean follow-up was 42 months (median 44; range=0-91 months) while two (4.7%) patients developed recurrent carcinoma; one patient received induction chemotherapy followed by pelvic irradiation and brachytherapy and the other underwent an abdominal hysterectomy with concomitant chemoradiotherapy and brachytherapy.

Three patients were excluded from the follow-up analysis. Patient 1 had residual disease within her second LLETZ and 12 negative pelvic nodes. After counseling, she refused fertility-sparing treatment and went for radical hysterectomy. Patient 2 had residual grade 2 squamous cell carcinoma on her repeat LLETZ with LVSI and 22 negative pelvic nodes. She also opted for radical hysterectomy, and after MDT discussion, she also received postoperative chemoradiotherapy. Patient 3 had a negative second LLETZ but 2 positive pelvic lymph nodes. She received chemoradiotherapy and subsequently passed away, due to radiation peritonitis.

Regarding the obstetric outcome, 16 (41.9%) patients became pregnant and 15 live births have been recorded. Four (9.3%) preterm deliveries were reported, with the earliest gestation at 32 weeks, while 1 (2.3%) had a first trimester miscarriage and another a first trimester termination of pregnancy. The authors concluded that this less radical fertility preservation technique for early stage cervical cancer should be adopted with caution, due to the fact that, even within this selected group of patients, 2 cases of central recurrent disease have been recorded (14).

Finally, conservative management of early stage cervical cancer was assessed by Ditto *et al.*, in a retrospective study of 22 young women, who underwent cervical conization and laparoscopic pelvic lymphadenectomy. Histology included 11 (50%) patients with adenocarcinoma, 10 (45%) with squamous cell carcinoma and 1 (5%) case with adenosquamous carcinoma of the cervix. Six (27%) and 16 patients had FIGO stage IA2 and IB1 (<2 cm), respectively. All patients were offered systematic laparoscopic pelvic lymphadenectomy without SLN mapping, and the mean number of lymph nodes removed was 26. Following primary treatment, 3 patients required NACT and radical surgery due to positive lymph nodes, while 1 patient (5%) asked for radical standard treatment, and she was offered a type B radical hysterectomy.

Mean follow-up was 48.8 months (range=2-128 months) and no recurrent disease was reported among patients who underwent conservative treatment. Recurrence was detected in 2 out of 3 patients with positive pelvic nodes who underwent radical hysterectomy; one patient presented with

lymph node relapse beyond the abdominal cavity, whereas another patient had recurrence in the para-aortic area.

From the reproductive point of view, 15 (83%) out of 18 women who preserved their fertility attempted to conceive, while 8 (53%) had spontaneous pregnancies. Obstetric outcome reported 4 (27%) term pregnancies, 1 (7%) preterm delivery at 32 weeks and 1 (7%) second-trimester miscarriage, while 2 patients were on an uneventful second-trimester pregnancy during their last follow-up visit. This study also highlights the long-term oncologic effectiveness of less radical approach to early stage cervical cancer (15).

Simple trachelectomy and pelvic lymphadenectomy. We found 15 articles regarding simple trachelectomy for early-stage cervical cancer in the past 5 years. Of these studies, we recorded 10 systematic reviews, 1 case report, 1 article in French and 3 articles were include in the present review, assessing the oncological and obstetrical outcomes of simple trachelectomy with pelvic lymphadenectomy as a fertility-sparing option for early stage cervical cancer.

Plante *et al.*, conducted a retrospective review of a prospective series of 35 women who underwent simple vaginal trachelectomy and laparoscopic sentinel lymph node mapping, followed by systematic pelvic lymphadenectomy. Based on FIGO staging, 8 patients had IA1 disease with LVSI, 9 had stage IA2 and 18 had stage IB1 disease. Histology indicated that they were 54% squamous carcinomas, 37% adenocarcinomas while 3 patients had other subtypes (clear cell, adenosquamous and undifferentiated). Diagnosis of the disease was made through cone biopsy in 9 patients, 17 had a LEEP, 6 had cervical biopsies and 3 patients had excision of a polyp, which turned out to be malignant on pathology. Invasive residual disease was reported in 13 patients (37%), while the margins in all trachelectomy specimens were negative.

Lymph node mapping was performed using either ^{99m}Tc and blue dye or indocyanine green. Twenty-eight (80%) patients had a systematic pelvic lymphadenectomy, with a median of 15 nodes removed per patient (range=5-30), 7 (20%) had sentinel lymph node mapping alone, with bilateral SLNs identified at surgery and negative frozen section, and in one case, SLN mapping was not performed.

Mean follow-up was 48 months (range=1-100 months) and 1 recurrence was reported in a patient with 2 positive pelvic lymph nodes. It was diagnosed on the left side of the cervix and parametrium through PET-CT and pelvic MRI. She underwent chemoradiation therapy, but due to persistent and unexplained pain, she was offered a definite hysterectomy and one year later no residual disease was identified in the specimen. Same patient presented with a new recurrence in the bladder site a few months later, for which she underwent a total pelvic exenteration.

Regarding the obstetric outcome, 25 pregnancies were reported, with 5 (20%) resulting in first trimester

Table II. Simple vaginal trachelectomy for early-stage cervical cancer.

Study	N	Figo stage	Histology	Procedure	LVSI	Recurrences	LNDs removed	Obstetrical outcome
Slama, 2016 (17)	32	IA2: 7 IB1: 23 IB2: 2	SCC: 21 Adenoca:3 Adenosq: 2	SVT: 11 Cone: 21	20	SVT: 2 Cone: 4	Not reported	Term: 4 Preterm:1 Miscarriage: 1
Plante, 2017 (16)	35	IA1+LVSI: 8 IA2: 9 IB1: 18	SCC:19 Adenoca: 13 Adenosq: 1 Clearcell: 1 Undif: 1	SVT: 35	9	1	15	Term: 18 Preterm: 2 Miscarriage: 5
Demirkiran, 2018 (18)	14	IA1+LVSI:3 IA2: 4 IB1: 7	SCC:12 Adenoca: 2	SVT: 13*	7	0	Not reported	Term: 4 Preterm: 2 Miscarriage: 1

miscarriages, 2 mild premature deliveries and 18 (72%) pregnancies ended at more than 36 weeks.

Based on this study, simple vaginal trachelectomy with pelvic lymphadenectomy seems a feasible alternative radical trachelectomy in a well selected group of patients with small-volume cervical cancer (16).

The efficacy and safety of simple vaginal trachelectomy or cone biopsy, combined with pelvic lymphadenectomy was assessed through a retrospective analysis by Slama *et al.*, which included women with cervical cancer stages IA2-IB2, under the age of 40. The procedure started with laparoscopic SLN mapping and complete pelvic lymphadenectomy and patients with negative nodes and tumors <2 cm were offered either needle conization or simple vaginal trachelectomy, while in larger tumors, neoadjuvant chemotherapy (NACT) was initially administered. Out of the 44 patients enrolled in the study, only 32 managed to complete fertility sparing surgery. The rest were not eligible due to positive lymph nodes (n=7), progression during NAC (n=2) or positive margins after excisional procedure, without the possibility of another re-excision (n=3).

Most of the patients were nulliparous (62.5%, 20/32) with squamous cell histology (81.3%, 26/32). NAC was offered in 9 (28.1%) cases, all of which had squamous cell carcinomas. Trachelectomy and needle conization was performed in 11 and 21 cases, respectively, while no patient required any adjuvant treatment. Mean follow-up was 23 months (range=3-53 months), during which 6 out of 32 women became pregnant (18.8%). Pregnancies resulted in 1 miscarriage, 4 term and 1 preterm delivery at 33 weeks. This study demonstrated that a significant number of patients (27%) cannot complete fertility sparing surgery due to lymph node positivity, progression during NAC or involved surgical margins. Total recurrence rate was 18.8%, mostly in patients after NAC followed by fertility-sparing surgery (FSS), showing the importance of careful patient selection, before proceeding to less radical fertility sparing surgery (17).

Recently, Demirkiran *et al.*, assessed the oncological safety of simple vaginal trachelectomy (SVT), combined with laparoscopic pelvic lymphadenectomy in a retrospective study of 14 patients with early-stage cervical cancer who wished to preserve their fertility. Laparoscopic SLN mapping using blue dye was performed in the beginning of the procedure, and nodes were sent for frozen section. Eight patients received a systematic pelvic lymphadenectomy, while 4 had SLN mapping alone. Thirteen out of 14 patients completed the fertility sparing surgery, while 1 patient was found with positive margins on final pathology and underwent a laparoscopic radical hysterectomy with ovarian transposition. No patient had lymph node metastasis. Follow-up was 27 months (range=6-56 months) and none of the 13 patients presented with a recurrence. Assessing the obstetric outcome, 11 patients attempted pregnancy and 7 conceived spontaneously. These pregnancies resulted to 4 term deliveries, 2 late preterm deliveries and 1 spontaneous abortion. Authors stated that this procedure seems to be a safe treatment option with excellent oncologic outcome, preserving reproductive potential (18) (Table II).

Discussion

Recent data suggest that nearly 40% of early cervical cancer is diagnosed in women of reproductive age. While radical trachelectomy represents a viable fertility-preserving option, the peri-operative morbidity along with the high rate of first- and second-trimester miscarriage (16-20% and 8-10% respectively) and preterm delivery (20-30%) reported for this method, has created the need to offer to a selected subgroup of these patients a less radical treatment (19-21).

A systematic review by Ramirez *et al.*, indicated that cervical conization or simple trachelectomy in a selected group of patients with early-stage cervical cancer (IA2-IB1), interested in future fertility, are acceptable options (10). Nonetheless, they should still be offered in the setting of a

Table III. Parametrial involvement in early-stage cervical cancer.

Study	N	FIGO stage	No of patients	LVSI		PI		Tumor size	No of patients
				No	Yes	No	Yes		
Baiocchi, 2017 (31)	345	IA2	13	228	103	329	16 ^a	≤2 cm	107
		IB1	273					>2 cm	190 ^b
		IB2	59						
Pareja, 2018 (32)	30	IA2	9	12	6	30	0	<10 mm	22
		IB1	21					10-20 mm	8

^aMissing data for 14 patients; ^bMissing data for 48 patients.

clinical trial and not in the daily routine clinical practice (10). Another systematic review by Reade *et al.*, presented similar results, highlighting the importance of sentinel lymph node biopsy, in an effort to reduce morbidity that follows systematic pelvic lymphadenectomy, in patients without nodal metastatic spread (22).

Tzafetas *et al.*, conducted a web-based survey about fertility-sparing surgical practice for early-stage cervical cancer in the United Kingdom. A total of 49 centers, members of the British Gynaecological Cancer Society participated in the survey. Results showed that, in the vast majority of centres (41/49, 83.7%), patients with stage IA2 and IB1 disease are offered simple conization and pelvic lymphadenectomy. This approach was performed in both stages in 25/49 centres (51.0%), whilst in 15/49 centres (30.7%), only in stage IA2 disease. These less radical techniques aim to improve future reproductive outcomes with an acceptable oncologic treatment (23).

Numerous analyses demonstrate that the incidence of parametrial involvement (PI) in patients with tumor size <2 cm, negative pelvic lymph nodes and depth of invasion <10 mm, was infrequent, and therefore a less radical approach could be justified (24-26). For this reason, there has been an increasing trend worldwide to manage low volume early stage disease with less radical approaches and omission of parametrectomy in an effort to reduce surgical morbidity and improve fertility outcome where eligible. Even for patients with small-volume stage IB1 cervical cancer that do not desire fertility preservation, treatment could be feasible with a less radical surgery, such as simple hysterectomy with bilateral lymph node dissection (27). In such cases, tumor volume is measured on the cone specimen, with the use of Burghardt's formula (28).

In a recent meta-analysis, Ma *et al.*, estimated the predictive value of LVSI and pelvic lymph node metastases (LNM) to PI, in a group of patients with presumed early stage cervical cancer. Twenty studies were included in this meta-analysis, 17 of which focused on the connection between LVSI and PI. LVSI status was identified from the

hysterectomy specimen and in 14 studies, LVSI was associated with PI, while 4 studies indicated LVSI as an independent factor for PI. The authors identified LNM and LVSI as risk factors for PI. The pooled sensitivity of LVSI and LNM was 0.80 and 0.90, respectively, stating these two study parameters as predictors of parametrial status. The authors stated that LVSI, which can be detected on conization specimens, is associated with PI and shows high sensitivity, while LNM shows high specificity. Therefore, the combination of conization and lymphadenectomy, apart from the therapeutic approach, could predict PI, in patients with early stage cervical cancer (25).

Wright *et al.*, demonstrated that the risk of PI is 6% and 48% in patients with negative and positive pelvic lymph nodes, respectively (29), while Covens *et al.*, reported that the risk for PI in patients with tumor size <2 cm, negative pelvic lymph nodes and depth of invasion <10 mm was 0.6%. The same study indicated that lymphovascular space invasion (LVSI) was strongly correlated with PI (30).

A retrospective study by Baiocchi *et al.*, included a series of 345 patients with stage IA2 to IB1 cervical cancer, for which they underwent radical surgery. Histology subtype indicated the presence of squamous cell carcinoma in 217 patients (62.9%) and the presence of adenocarcinoma or adenosquamous carcinoma in 128 patients (37.1%). The study demonstrated that 1.3% of patients without LVSI had PI, compared to 12.6% with LVSI ($p<0.001$). Regarding lymph node assessment, the percentage of patients with positive and negative lymph nodes that presented with PI was 21.2% and 1.7%, respectively. Furthermore, 68.7% of patients with PI had positive lymph nodes and 81.2% of them had LVSI. However, PI was absent in patients with tumors ≤2 cm and negative lymph nodes (31).

Pareja *et al.*, attempted to identify predictive factors in patients with a diagnosis of occult cervical cancer after simple hysterectomy for benign gynecologic conditions or preinvasive cancer lesions. The study included 30 patients with tumors <2 cm in the initial surgery specimen. All patients received subsequent radical parametrectomy by

laparotomy, robot-assisted laparoscopy and laparoscopy; 66.7%, 26.7% and 6.7%, respectively. The pathology report after radical parametrectomy stated no residual tumor, PI, vaginal tissue or lymph node metastasis, regardless of tumor size, while none of the patients required adjuvant chemotherapy or radiotherapy. The authors concluded that radical parametrectomy could be avoided in patients with low-risk early-stage cervical cancer detected after a simple hysterectomy (32) (Table III).

A review and meta-analysis of observational studies that was conducted by Zhang *et al.*, assessed the oncological and obstetrical outcomes in patients with early-stage cervical cancer, treated with conization or RT, with or without systematic pelvic lymphadenectomy. A total of 60 studies were analyzed, 17 of which referred to conization and 43 reported on RT with 375 and 2,479 patients, respectively.

Regarding the group of patients that underwent cervical conization, 176 (46.9%) had FIGO stage IA1, 30 (8%) had stage IA2, 167 (44.5%) had stage IB1, 1 patient (0.27%) presented with stage IB2 and 1 (0.27%) with stage IIA disease. No details were provided on the presence of LVSI or histological subtype. Follow-up ranged from 16 to 81 months and the authors reported 4 relapses, with a mortality rate of 0%. Meta-analysis of the cervical conization cases reported a pregnancy rate of 36.1%, miscarriage rate of 14.8% and preterm delivery rate of 6.8%. As comparison, the RT group referred to 143 cases (6%) with FIGO stage IA1, 299 cases (12.1%) with stage IA2 and 1987 cases (79.9%) with stage IB1 cervical cancer. Pregnancy rate was 20.5%, first- or second-trimester miscarriage rate was recorded at 24% and preterm delivery rate was 26.6%. Again, the authors concluded that less radical approach to early stage cervical cancer should be reserved for a carefully selected group of patients with favorable prognostic factors (33).

The feasibility of a less radical approach to early-stage cervical cancer is under evaluation by ongoing prospective clinical trials; the SHAPE trial, the ConCerv trial and the Gynecologic Oncology Group protocol 278 trial.

The management of cervical cancer has evolved significantly in the last decades. Early-stage and small size cervical cancer is nowadays being regarded manageable with a less radical approach, to reduce surgery related impact on long term QoL and functionality with a potentially questionable survival benefit. It appears from numerous non-randomized data, that omission of parametrectomy may be safe in a subcohort of patients with favorable tumor characteristics. While awaiting the results of currently recruiting prospective randomized clinical trials to demonstrate the safety of such an approach, potentially eligible patients for a less radical surgical treatment should be thoroughly informed about their therapeutic options and the associated risks and benefits and be referred to specialized cancer centers.

Conflicts of Interest

The Authors declare no conflicts of interest related to this study.

Authors' Contributions

CT wrote the manuscript, DH and NT edited and highlighted the corrections and AR and CP approved the manuscript.

References

- 1 American Cancer Society 2017. What Are the Key Statistics About Cervical Cancer. Available at: <https://www.cancer.org/cancer/cervical-cancer/about/key-statistics.html>
- 2 Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D and Bray F: Cancer incidence and mortality worldwide: Sources, methods and major patterns in globocan 2012. *Int J Cancer* 136(5): E359-386, 2015. PMID: 25220842. DOI: 10.1002/ijc.29210
- 3 Otter S, Whitaker S, Chatterjee J and Stewart A: The human papillomavirus as a common pathogen in oropharyngeal, anal and cervical cancers. *Clin Oncol (R Coll Radiol)*, 2018. PMID: 30385006. DOI: 10.1016/j.clon.2018.10.004
- 4 Maneo A, Sideri M, Scambia G, Boveri S, Dell'anna T, Villa M, Parma G, Fagotti A, Fanfani F and Landoni F: Simple conization and lymphadenectomy for the conservative treatment of stage ib1 cervical cancer. An italian experience. *Gynecol Oncol* 123(3): 557-560, 2011. PMID: 21907396. DOI: 10.1016/j.ygyno.2011.08.009
- 5 Fagotti A, Gagliardi ML, Moruzzi C, Carone V, Scambia G and Fanfani F: Excisional cone as fertility-sparing treatment in early-stage cervical cancer. *Fertil Steril* 95(3): 1109-1112, 2011. PMID: 21122837. DOI: 10.1016/j.fertnstert.2010.11.010
- 6 Frumovitz M, Sun CC, Schover LR, Munsell MF, Jhingran A, Wharton JT, Eifel P, Bevers TB, Levenback CF, Gershenson DM and Bodurka DC: Quality of life and sexual functioning in cervical cancer survivors. *J Clin Oncol* 23(30): 7428-7436, 2005. PMID: 16234510. DOI: 10.1200/JCO.2004.00.3996
- 7 Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P, Favini G, Ferri L and Mangioni C: Randomised study of radical surgery versus radiotherapy for stage ib-iiia cervical cancer. *Lancet* 350(9077): 535-540, 1997. PMID: 9284774. DOI: 10.1016/S0140-6736(97)02250-2
- 8 Dargent D and Mathevet P: Schauta's vaginal hysterectomy combined with laparoscopic lymphadenectomy. *Baillieres Clin Obstet Gynaecol* 9(4): 691-705, 1995. PMID: 8821248. DOI: 10.1016/s0950-3552(05)80392-x
- 9 Plante M, Gregoire J, Renaud MC and Roy M: The vaginal radical trachelectomy: An update of a series of 125 cases and 106 pregnancies. *Gynecol Oncol* 121(2): 290-297, 2011. PMID: 21255824. DOI: 10.1016/j.ygyno.2010.12.345
- 10 Ramirez PT, Pareja R, Rendon GJ, Millan C, Frumovitz M and Schmeler KM: Management of low-risk early-stage cervical cancer: Should conization, simple trachelectomy, or simple hysterectomy replace radical surgery as the new standard of care? *Gynecol Oncol* 132(1): 254-259, 2014. PMID: 4286394. DOI: 10.1016/j.ygyno.2013.09.004
- 11 Bouchard-Fortier G, Reade CJ and Covens A: Non-radical surgery for small early-stage cervical cancer. Is it time? *Gynecol*

- Oncol 132(3): 624-627, 2014. PMID: 24480237. DOI: 10.1016/j.ygyno.2014.01.037
- 12 Tomao F, Maruccio M, Preti EP, Boveri S, Ricciardi E, Zanagnolo V and Landoni F: Conization in early stage cervical cancer: Pattern of recurrence in a 10-year single-institution experience. *Int J Gynecol Cancer* 27(5): 1001-1008, 2017. PMID: 28486242. DOI: 10.1097/IGC.0000000000000991
- 13 Andikyan V, Khoury-Collado F, Denesopolis J, Park KJ, Hussein YR, Brown CL, Sonoda Y, Chi DS, Barakat RR and Abu-Rustum NR: Cervical conization and sentinel lymph node mapping in the treatment of stage i cervical cancer: Is less enough? *Int J Gynecol Cancer* 24(1): 113-117, 2014. PMID: 4972180. DOI: 10.1097/IGC.0000000000000034
- 14 Lindsay R, Burton K, Shambhag S, Tolhurst J, Millan D and Siddiqui N: Fertility conserving management of early cervical cancer: Our experience of Iletz and pelvic lymph node dissection. *Int J Gynecol Cancer* 24(1): 118-123, 2014. PMID: 24300465. DOI: 10.1097/IGC.0000000000000023
- 15 Ditto A, Martinelli F, Bogani G, Fischetti M, Di Donato V, Lorusso D and Raspagliesi F: Fertility-sparing surgery in early-stage cervical cancer patients: Oncologic and reproductive outcomes. *Int J Gynecol Cancer* 25(3): 493-497, 2015. PMID: 25628110. DOI: 10.1097/IGC.0000000000000371
- 16 Plante M, Renaud MC, Sebastianelli A and Gregoire J: Simple vaginal trachelectomy: A valuable fertility-preserving option in early-stage cervical cancer. *Int J Gynecol Cancer* 27(5): 1021-1027, 2017. PMID: 28498240. DOI: 10.1097/IGC.0000000000000989
- 17 Slama J, Cerny A, Dusek L, Fischerova D, Zikan M, Kocian R, Germanova A and Cibula D: Results of less radical fertility-sparing procedures with omitted parametrectomy for cervical cancer: 5 years of experience. *Gynecol Oncol* 142(3): 401-404, 2016. PMID: 27396943. DOI: 10.1016/j.ygyno.2016.07.008
- 18 Demirkiran F, Kahramanoglu I, Bese T, Turan H, Meseci E and Arvas M: Simple vaginal trachelectomy for early stage cervical cancer: A tertiary cancer center experience. *Ginekolo Pol* 89(9): 475-480, 2018. PMID: 30318573. DOI: 10.5603/GP.a2018.0081
- 19 Beiner ME and Covens A: Surgery insight: Radical vaginal trachelectomy as a method of fertility preservation for cervical cancer. *Nat Clin Pract Oncol* 4(6): 353-361, 2007. PMID: 17534391. DOI: 10.1038/ncponc0822
- 20 Gien LT and Covens A: Fertility-sparing options for early stage cervical cancer. *Gynecol Oncol* 117(2): 350-357, 2010. PMID: 20163850. DOI: 10.1016/j.ygyno.2010.01.039
- 21 Sonoda Y, Abu-Rustum NR, Gemignani ML, Chi DS, Brown CL, Poyner EA and Barakat RR: A fertility-sparing alternative to radical hysterectomy: How many patients may be eligible? *Gynecol Oncol* 95(3): 534-538, 2004. PMID: 15581959. DOI: 10.1016/j.ygyno.2004.07.060
- 22 Reade CJ, Eiriksson LR and Covens A: Surgery for early stage cervical cancer: How radical should it be? *Gynecol Oncol* 131(1): 222-230, 2013. PMID: 23863357. DOI: 10.1016/j.ygyno.2013.07.078
- 23 Tzafetas M, Mitra A, Kalliala I, Lever S, Fotopoulou C, Farthing A, Smith JR, Martin-Hirsch P, Paraskevaidis E and Kyrgiou M: Fertility-sparing surgery for presumed early-stage invasive cervical cancer: A survey of practice in the united kingdom. *Anticancer Res* 38(6): 3641-3646, 2018. PMID: 29848721. DOI: 10.21873/anticancer.12639
- 24 Steed H, Capstick V, Schepansky A, Honore L, Hiltz M and Faught W: Early cervical cancer and parametrial involvement: Is it significant? *Gynecol Oncol* 103(1): 53-57, 2006. PMID: 16516279. DOI: 10.1016/j.ygyno.2006.01.027
- 25 Ma C, Zhang Y, Li R, Mao H and Liu P: Risk of parametrial invasion in women with early stage cervical cancer: A meta-analysis. *Arch Gynecol Obstet*, 2017. PMID: 29177590. DOI: 10.1007/s00404-017-4597-0
- 26 Schmeler KM, Frumovitz M and Ramirez PT: Conservative management of early stage cervical cancer: Is there a role for less radical surgery? *Gynecol Oncol* 120(3): 321-325, 2011. PMID: 21320670. DOI: 10.1016/j.ygyno.2010.12.352
- 27 Biliatis I, Kucukmetin A, Patel A, Ratnavelu N, Cross P, Chattopadhyay S, Galaal K and Naik R: Small volume stage 1b1 cervical cancer: Is radical surgery still necessary? *Gynecol Oncol* 126(1): 73-77, 2012. PMID: 22465521. DOI: 10.1016/j.ygyno.2012.03.041
- 28 Haas J: Tumormetry. *In: Surgical gynecologic oncology*. 1st ed. Burghardt E (ed.). Thieme Medical Publishers Inc: New York, pp. 241-243, 1992.
- 29 Wright JD, Grigsby PW, Brooks R, Powell MA, Gibb RK, Gao F, Rader JS and Mutch DG: Utility of parametrectomy for early stage cervical cancer treated with radical hysterectomy. *Cancer* 110(6): 1281-1286, 2007. PMID: 17654664. DOI: 10.1002/cncr.22899
- 30 Covens A, Rosen B, Murphy J, Laframboise S, DePetrillo AD, Lickrish G, Colgan T, Chapman W and Shaw P: How important is removal of the parametrium at surgery for carcinoma of the cervix? *Gynecol Oncol* 84(1): 145-149, 2002. PMID: 11748991. DOI: 10.1006/gyno.2001.6493
- 31 Baiocchi G, de Brot L, Faloppa CC, Mantoan H, Duque MR, Badiglian-Filho L, da Costa A and Kumagai LY: Is parametrectomy always necessary in early-stage cervical cancer? *Gynecol Oncol* 146(1): 16-19, 2017. PMID: 28392128. DOI: 10.1016/j.ygyno.2017.03.514
- 32 Pareja R, Echeverri L, Rendon G, Munsell M, Gonzalez-Comadran M, Sanabria D, Isla D, Frumovitz M and Ramirez PT: Radical parametrectomy after 'cut-through' hysterectomy in low-risk early-stage cervical cancer: Time to consider this procedure obsolete. *Gynecol Oncol* 149(3): 520-524, 2018. PMID: 29482838. DOI: 10.1016/j.ygyno.2018.02.015
- 33 Zhang Q, Li W, Kanis MJ, Qi G, Li M, Yang X and Kong B: Oncologic and obstetrical outcomes with fertility-sparing treatment of cervical cancer: A systematic review and meta-analysis. *Oncotarget* 8(28): 46580-46592, 2017. PMID: 5542294. DOI: 10.18632/oncotarget.16233

Received May 27, 2020

Revised June 16, 2020

Accepted June 19, 2020