

# Sexual and Reproductive Outcomes in Early Stage Cervical Cancer Patients after Excisional Cone as a Fertility-sparing Surgery: An Italian Experience

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## Abstract

**Background:** The purpose of this study was to analyze the quality of life in terms of sexual and reproductive outcome in patients suffering from early stage cervical cancer, submitted to an excisional cone as fertility-sparing treatment.

**Methods:** A multicenter retrospective analysis about specific dimensions of physical, psychological, reproductive and sexual functions after a cold-knife conization plus pelvic laparoscopic lymphadenectomy was conducted at Division of Gynecologic Oncology, Catholic University of the Sacred Heart, Rome-Italy and at Division of Gynecology, European Institute of Oncology, Milan-Italy. The aim of this study was twofold. It aimed to analyze the quality of life in patients submitted to minimally invasive surgery and to compare these data with radical trachelectomy.

**Results:** Twenty-three patients with an average age of 30 years decided to participate in this study. After the treatment, all women (100%) had regular menstruation, 7 (30.4%) had increased not invalidating dysmenorrhea; 1 (4.4%) experienced a cervical stenosis; 6 among 10 patients that tried to conceive (60%) obtained one spontaneous pregnancy; 4 more (40%) underwent *in vitro* fertilization and embryo transfer and only 1 of them (25%) was successful. About sexual assessment, 1 patient (4.4%) had trouble in lubricating, 3 (13%) had anxiety about performance, 6 (26.1%) complained of dyspareunia which was resolved within 3 subsequent months. All patients (100%) obtained a complete psychological and physical recovery.

**Conclusion:** This study demonstrated preliminary encouraging data about sexual and reproductive outcome after excisional conization. A comparison with trachelectomy surely needs longer follow-ups, more cases and prospective analyses.

**Keywords:** Cervical cancer, Conservative approach, Excisional cone, Fertility-sparing surgery, Quality of life.

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## Introduction

Young patients with Early stage Cervical Cancer (ECC) are potential candidates for fertility-sparing surgery, once their specific risks are assessed. Until now, the majority of experiences in this field were focused on radical trache-

lectomy which help in preserving the uterus and maintain adequate survival outcomes (1–5). Moreover, the suture of the isthmus to the vaginal wall may seriously impair both pregnancy rate and uterine continence, with a high rate of first-

and second-trimester miscarriage (16–20% and 8–10%, respectively) and preterm delivery (20–30%) (3).

In order to improve the obstetric outcomes, we proposed a less invasive fertility-sparing treatment in a consecutive series of young women with ECC including excisional cone, pelvic laparoscopic lymphadenectomy and eventual neo- or adjuvant chemotherapy (6–8). Preliminary findings have demonstrated the feasibility of this treatment offering possibly better obstetric outcomes than trachelectomy.

Cervical cancer remains an important health problem, even though improved screening, new treatment knowledge and earlier stage cases, improve the number of long-term survivors (9). Moreover, in the last years, NCI (National Cancer Institute) and FDA (Food and Drug Administration) recognized that Quality of Life (QOL) assessment is an essential element in surgical and clinical care, along with other traditional ones (10–12). QOL makes reference to the general well-being of individuals; the term is used in a wide range of contexts. It also allows for objective comparisons to be made between the situations of particular groups and what is normative. There is a general consensus that quality of life is multidimensional. A substantial body of literature supports the need to examine it among cervical cancer women managed either with radical or conservative treatment (9, 13).

Long-term post-operative sexual and reproductive outcomes can have an effect on physical, psychological and social issues; furthermore, women managed with a fertility-sparing surgery can increase the problems concerned with their reproductive ability.

To our knowledge, post-operative sexual and reproductive outcome of ECC patients who underwent fertility-sparing has been investigated only after radical trachelectomy (14–16). We conducted this multicenter Italian study in ECC women experienced fertility-sparing after conization in order to analyze the post-operative QOL in terms of sexual and reproductive outcome of patients submitted to this new minimally invasive surgery and secondly compare these data with those reported for radical trachelectomy.

### Methods

**Study design and recruitment:** Between May 2002 and September 2011, 30 consecutive women <45

year old with ECC (FIGO stage IA2-IB1  $\leq 2$  cm tumor size) (17) were managed with a fertility-sparing treatment consisting of excisional cone and laparoscopic pelvic lymphadenectomy, as previously described (6–8), into two Italian centers: Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Catholic University of the Sacred Heart, Rome-Italy (19 patients); Division of Gynecology, European Institute of Oncology, Milan-Italy (11 patients).

Women were eligible to participate in this study if they: 1. Currently received no cancer therapy; 2. Were free from the disease; 3. Had no other history of cancer; 4. Were not submitted to a surgical radicalization (*ie.* trachelectomy or hysterectomy).

Patients were contacted by telephone, and to those who agreed to participate, questionnaires with informed consent and postage-paid return envelopes were sent. They were informed that non-participation in this study would not interfere with their follow-up care. Institutional review board approval of each center was obtained.

**Cases:** Of 30 women identified for this study, 23 (76.7%) provided signed informed consent and completed the questionnaire. Four patients (13.3%) were submitted to a radical hysterectomy after fertility-sparing conization and 3 women (10%) declined. Of the 30 women, 4 (13.3%) were submitted to neoadjuvant chemotherapy and 1 (3.3%) to three cycles of platinum-based adjuvant chemotherapy.

**Measures:** The questionnaire included socio demographic characteristics, medical and cancer history, and instruments that assessed specific dimensions of physical, psychological, reproductive and sexual functions. Variables of interest were the following:

1. Menstrual characteristics, in terms of quantity/duration/regularity; eventual intermenstrual bleeding/spotting; eventual increased and/or new (newly diagnosed) dysmenorrhea
2. Recurrent vaginal and/or urinary infections
3. Sexual problems such as dyspareunia, trouble in lubricating, anxiety about performance, lack of libido
4. Reproductive concerns (anxiety for a pregnancy, eventual impact of cancer history on baby, anxiety about a recurrence during pregnancy, inability to conceive)
5. All data about an eventual pregnancy after the treatment
6. Concerns about choosing this fertility-sparing

treatment

7. Time of psychological and physical recovery (quantified in months)

**Statistical analysis:** Descriptive statistics and qualitative analysis were performed on the study items. Continuous data are presented as median and range. Categorical variables are reported as absolute values and percentages.

### Results

**Demographic and health variables:** Participants' ages ranged from 24 to 43 years (average=30). At the time of the study enrollment, over half of the patients were married/or common-law partners (65.2%, n=15); approximately one-third were single (34, 8%, n=8) and 26.1% (n=6) had children at enrollment. All pregnancies were obtained after the fertility-sparing treatment. Table 1 presents further demographic and medical characteristics.

**Post-operative data:** Specific items in the post-operative time were assessed after a median fol-

**Table 1.** Characteristics of study population

Characteristics	n=23
Median age, year (range)	30 (24–43)
BMI, kg/m <sup>2</sup> (range)	22 (19–25)
<b>FIGO stage</b>	
IA2, n (%)	7 (30.4)
IB1, n (%)	16 (69.6)
Median tumoral diameter, mm (range)	15 (3–20)
<b>Hystopathological type</b>	
Squamous cell carcinoma, n (%)	11 (47.8)
Adenocarcinoma, n (%)	11 (47.8)
Glassy cell tumor, n (%)	1 (4.4)
<b>Hystopathological grading</b>	
G1, n (%)	10 (43.5)
G2, n (%)	10 (43.5)
G3, n (%)	3 (13)
Median number of pelvic nodes removed (range)	18 (10–52)
<b>Marital status</b>	
Single, n (%)	8 (34.8)
Married or common-law partner, n (%)	15 (65.2)
<b>Education</b>	
Low, n (%)	5 (21.7)
High school, n (%)	6 (26.1)
Graduation, n (%)	12 (52.2)
<b>Ethnicity</b>	
Hispanic, n (%)	11 (47.8)
Non-Hispanic, n (%)	12 (52.2)

**Table 2.** Frequency of answer to questions about quality of life

Answer to questionnaire	Percentage (%)
Problems related menstruation	10
Recurrent vaginal or urinary infections	7
Sexual problems	5
Concerns about pregnancy	11
Total number of pregnancies	7
Spontaneous pregnancies	6
Cervical cerclages	1
Miscarriages	0
Preterm deliveries	1
Term deliveries	5
Psychological and physical delay	23
Concerns about choosing this treatment	0

low-up of 40 months (range 32–125 months). A schematic synopsis of QOL assessment is showed in (Table 2).

After surgery, all women (100%) had regular menstruation after a median time of 30 days (range 2–60 days); overall, 7 (30.4%) had increased dysmenorrhea responsive to medical treatment, 1 (4.4%) had hypermenorrhea, 2 (8.7%) premenstrual spotting and 7 (30.4%) recurrent vaginitis.

About sexual assessment, 1 (4.4%) had trouble in lubricating, 3 (13%) had anxiety about performance, 6 (26.1%) complained of dyspareunia which was resolved within 3 subsequent months.

One patient (4.4%) experienced dysmenorrhea secondary to cervical stenosis and it was successfully managed with dilation under local anesthesia.

Ten (43.5%) women tried to conceive; in particular, 4 (40%) after 3 months, 3 (30%) after 12 months, 1 (10%) after 18 months, 1 (10%) after 24 months and 1 (10%) after 48 months. Overall, 11 (47.8%) showed concerns about a future pregnancy, of whom 7 (30.4%) had a fear of possible inability to conceive, 1 (4.4%) to maintain the pregnancy, 2 (8.7%) to have a recurrence during the pregnancy and 1 (4.4%) had the fear of possible negative impact of their cancer history on the baby.

Globally, 5 out of 10 patients who tried to conceive (50%) obtained one spontaneous pregnancy; 4 more (40%) tried the IVF-ET (*in vitro* fertilization-embryo transfer) once or twice and only 1 patient (25%) was successful. 1 patient (16.7%) needed a cervical cerclage; and the pregnancy ob-

tained with IVF-ET was managed with an elective cesarean section at 33 weeks due to complications related to preeclampsia and placenta previa. Others pregnancies (83.3%) ended in the term and spontaneous delivery; babies currently enjoy good health. No miscarriage was recorded.

Sixteen women (69.6%) had an immediate psychological and physical recovery, 4 (17.4%) after 3 months and 2 (8.7%) after 12 months. No patient wrote to have concerns about choosing this fertility-sparing treatment. No recurrence of disease was recorded.

### Discussion

Fertility-sparing surgery is a possibility for young ECC women that wish to preserve their reproductive function, but as is the case with any oncological surgery, physical and emotional ramifications exist. Today, regarding matching specific inclusion criteria for ECC patients (3), two surgical fertility-sparing options are reported in the literature: trachelectomy plus pelvic lymphadenectomy (1) or conization plus pelvic lymphadenectomy (6–8, 18–20).

A consistent body of literature focused on oncologic and QOL results after trachelectomy, which was the first proposed fertility-sparing surgery (1) and that showed a safety in terms of radicality and recurrence rate (3, 21). In well-selected cases, conization results in lower surgical invasiveness and helps to avoid the side effects of parametrectomy and improves the obstetric outcomes (6–8). Moreover, after a median follow-up of 40 months (range 32–125 months), we observed no recurrence of the disease; in the longer follow-up of Maneo et al. (22), only 1 out of 36 (2.8%) pelvic lymph-nodal relapse was reported. These data show oncologic safety of this surgical treatment as well.

Several medical chart reviews, clinical feedback and preliminary data from prospective studies identified that after trachelectomy, patients experience a great number of post-operative issues (9). When trying to find inciting factors for these post-operative issues, vaginal scarring and neo-cervical encroachment were immediately identified (15). Cervical stenosis, which is associated with the volume of tissue resected and/or history of previous excisions, may lead to menstrual problem, dyspareunia and infertility or subfertility (14–16).

Many cervical cancer survivors managed with trachelectomy, reported distress and worries about

conception and pregnancy, which lasted up to 6 months post surgery (9, 14–16).

Our paper reflects preliminary data of a retrospective analysis collecting information from newly diagnosed ECC patients managed with conization. As showed in Figure 1, although conization offers the hope of future fertility, about half of the patients had reproductive concerns about their possible inability to conceive. These concerns are equally reported after trachelectomy (14–16); in fact, the uncertainty about conception and acknowledgement of a high-risk pregnancy may place women at risk for emotional sequels. Moreover, only half of the patients tried to obtain a pregnancy; as previously reported (8), majority of women did not have an immediate desire for pregnancy, but their desire for fertility-sparing is often related to their future anxiety and is independent from the type of fertility-sparing surgery proposed.

About menstrual problems, no patient experienced significant changes in duration/regularity/quantity of menstruation and also dysmenorrhea. Moreover, specific problematic issues of trachelectomy are related to cervical stenosis, encroachment, agglutination and vaginal scarring. Carter et al. (15) reported over 30 patients managed with trachelectomy and submitted to a prospective QOL analysis, 33% of women with clinically notable stenosis not requiring dilation and 40% requiring it; moreover, it was reported that a high rate of sexual inactivity tended to decrease if dyspareunia diminished over time. Wenzel et al. (9) reported 4 divorces out of 9 (44.4%) due to the cancer and its consequences.

We had only 1 (4.4%) case of cervical stenosis resolved under local anesthesia, and only 1 (4.4%) of the patients had no more sex since her partner refused. None had prolonged dyspareunia or trouble in lubricating, probably because of their less invasive surgery that allowed preserving the superior third of the vagina, part of the cervix and the paracervix. Also considering the low numbers of cases, sexual and reproductive outcome of conization are superior to those reported for trachelectomy (14, 16).

Another important issue is that 5 out of 6 pregnancies (83.3%) ended in term vaginal delivery, without any case of miscarriage and with healthy babies; the only pre-term cesarean section was due to preeclampsia that may be one of the negative consequences of IVF-ET (23). Three more

unsuccessful IVF-ETs could suggest the absence of any association with cervical factor infertility. Interestingly, none wrote to have any concerns about choosing this fertility-sparing treatment.

### Conclusion

The preliminary results of this analysis are encouraging, although it is a retrospective study and therefore subject to recall bias; data cannot be compared with those resulting from a prospective one. Therefore, we recommend that caution should be taken in the interpretation of these results.

On the other hand, this is the first study about the topic among a homogeneous group of highly educated women.

Surely, the first objective of a modern gynecologic oncologist must be offering a safe fertility-sparing surgery to a well-selected ECC population. On the other hand, QOL cannot be a secondary endpoint anymore; further studies need to confirm whether a less invasive surgery in comparison to trachelectomy could have immediate or long-term improvement in QOL

### Conflict of Interest

The authors have no conflicts of interest to declare.

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