

Fertility preservation in women with early stage cervical cancer.

Review of the literature

I. Boutas, C. Sofoudis, E. Kalampokas, C. Anastasopoulos, T. Kalampokas, N. Salakos

*2nd Department of Obstetrics and Gynecology, University of Athens, Aretaieion Hospital,
Department of Gynecological Oncology, Athens (Greece)*

Summary

Within the last decades, the percentage of diagnosed cervical cancer in women of reproductive age has increased. The possibility of diagnosing small cervical tumors (\leq two cm) in childbearing age, can be explained due to the fact that many women, are aware of the benefits of Pap smear or colposcopy examination. Many demand a more conservative policy to handle such lesions in order to have an uneventful pregnancy in the near future.

Key words: Cervical cancer; Trachelectomy; Fertility.

Introduction

Although it can be perceived that cancer is the disease of elderly women, a significant percentage reveals the opposite. Forty percent of women with diagnosed cervical cancer are in the reproductive age [1]. Nowadays, cervical cancer is considered to be the second most common malignancy in women in developing countries and the seventh in developed countries [2]. Twenty-two percent of the new diagnosed cases each year are indicated in women under the age of forty-five years.

In order to maintain life quality, women with cervical cancer, especially in early ages, focus on the preservation of fertility and by extension childbearing.

Worthy mentioning indeed, the frequency of diagnosed cervical cancer in women of reproductive age has become very conventional in the last two decades. The frequency of diagnosed cervical cancer in women of reproductive age has become very conventional in the last two decades. The increased diagnosis of small cervical tumors (\leq two cm) in childbearing age, even in nulliparus patients, can be explained due to the fact that many women, nowadays, are aware of the benefits of Pap smear or colposcopy examination and of the early symptoms of this disease. As a conclusion, many of them demand a more conservative treatment to handle such lesions.

In modern societies even more women are postponing maternity until their mid and late 30s, owed to social and personal reasons such as career achievements. This leads to a considerable number of women who will develop early invasive cancer of the cervix without fulfilling their personal thoughts of maternity. Therefore gynecologists should take under consideration the need of fertility sparing surgery in suitable cases.

In 1948, Franz Novak in Ljubljana apprehended a vaginal trachelectomy. The word trachelectomy has its roots in the ancient Greek idiom from the word “trachelos” meaning cervix [3]. Later in 1956, Aburel [4] circumscribed an abdominal approach with the removal of cervix. In the 1970s, however, Burghardt and Holzer [5] perceived that the removal of the corpus uteri was not indispensable in all cases of small early invasive cancer.

Dargent *et al.* [6] presented in 1994 more references for uterine conservation. Through the vaginal route they excised the cervix with the para-cervical and upper vaginal tissues and simultaneously a laparoscopic pelvic-node dissection was executed.

Shephert *et al.* [7] and Roy and Plant [8] amended this approach with felicitous outcomes. The abdominal approach in combination with a pelvic-node dissection was re-introduced in 2005 by Ungar *et al.* [9].

The traditional therapeutic choice for cervical cancer is either surgically with radical hysterectomy or with radiation. Neither of these options preserves the function of the utero-ovarian system, which is requisite for reproduction. As far as the more advanced stage disease is concerned, the management remains the same. On the contrary, for the early-staged cervical cancer it has been concluded in the past two decades, that fertility preservation can be achieved without compromising oncologic outcomes [10-15].

Staging of cervical cancer

The procedure of staging cervical cancer is performed under anaesthesia with accessional data from imaging techniques including chest radiography and an intravenous program computerized axial tomography (CT). In order to detect para-aortic lymph nodes abdominal and cervical scanning are widely used. This scanning offers a high specificity and low sensitivity [16].

In assessing pelvic nodes disease, magnetic resonance imaging (MRI) has demonstrated to be as precise as CT, and the results for

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primary tumours within the cervix with MRI are more accurate and concrete. Moreover it evaluates the parametrial tumor spread by different imaging [17, 18] and also permits the assessment of pelvic lymph nodes [19, 20].

MRI imaging provides several benefits such as the measurement of the size of the tumour, the location and the distance from the isthmus, and the assessment of the endocervical canal and the uterine cavity. The available accuracy of the endovaginal coil with MRI imaging permits the acquisition of better definition of the tumour and the involvement of the cervix with the inner portion of the paracervical and paravaginal tissues [19].

A specific examination under anaesthesia and an updated patient's history as far as the histology obtained from previous biopsies are required for the evaluation of the fertility sparing surgery. MRI assists in the selection of the patient by careful assessment of the cervix and the paracervical tissues [21] for the precise staging of the tumour [22].

The detection of pelvic lymph node metastases remains laborious and lymphangiography which was common for many years, has been abandoned. Some gynecologists advocate the sentinel node detection [23, 24]. Immunocytochemistry [25] performs the detection of circulating tumours cells and micrometastases in sentinel nodes. Worth mentioning are the accurate results that the combining laparoscopy with lymphoscintigraphy offers in sentinel node mapping [26]. Furthermore, molecular imaging has been described and shown to have enthralling possibilities in the detection of micrometastases by the use of ultrasmall iron oxide particles [27].

Patients' characteristics

The management of fertility sparing surgery must subsume a special group of patients carefully chosen and a well-informed background on them. The briefing about the preoperative examinations, the surgery, the postoperative complications, and especially about the risk of a premature delivery is indeed necessary. The patient must be aware of the risk that she will probably face in future pregnancies and about the need of alteration of her daily lifestyle activities [28-31].

The main criterion in all health centers remains the strong desire of fertility and maternity. The preservation of the uterus is controversial in patients who are not willing a future pregnancy and they ask for the preservation only for personal reasons [32, 33].

Surgical methods for fertility preservation

The primary lesion as well as the potential metastases must be involved in treatment for invasive cancer. The initial treatment varies, due to the extent of the disease and the diversity of the patients.

The most common management for early stage cancer is the definitive surgery. However, in terms of primary treatment radiation therapy may also be used. Both these managements offer equal effectiveness in the treatment of early cervical malignancies. More advanced cases are usually treated with combination radio-chemotherapy [34].

The option of the fertility preservation depends on the staging of the cancer. Stage IA1 cervical cancer, which defined as an invasion of less than three-mm depth of stromal invasion and less than seven-mm horizontally, is considered as the earliest stage of cancer [35].

The treatment suitable for young women wishing to preserve fertility is a cone biopsy. Cone biopsy is considered as the most established method due to the accurate assessing of the cervical tumour. It can be performed either by cold knife or diathermy, or by large loop excision of the transformation zone or loop electrosurgical procedure.

The surgical guidelines can be given by the depth and the diameter of the lesion with a 3D measurement. The therapeutic choice for small, superficially invasive tumours, Stage IA1 and even IAII, is considered to be cone biopsy. Therefore no further treatment is required. The margins of excision must be clear in both invasive and high-grade pre-invasive intraepithelial neoplasia.

A simple hysterectomy, namely the removal of the uterus and the cervix without the ovaries and the fallopian tubes, is mostly performed for this stage of cancer. However, if the patient desires to preserve fertility, she must be aware that the approach of cone biopsy is not the standard one.

During the cone biopsy an endocervical sampling is conducted. It is very useful that the surgery confirms the depth of the invasion (less than three mm of stromal invasion and less than seven mm horizontally) in order to dodge more extensive surgeries. The patient can be followed closely, only if the endocervical canal curettage sample is negative, as well as all the margins [36].

In order to preserve an ensuing pregnancy and avoid premature delivery, a cervical suture may be necessary, although it may increase the risk of cervical incompetence, depending on the risk of the internal orifice and on how high the excision has been carried out.

There are options for women with microinvasive disease, classified as IAII to IB1, willing to preserve fertility. Radical hysterectomy is the main therapeutic management for patients following lymph node dissection. A radical hysterectomy removes the uterus and the cervix as well as the surrounding parametrial tissue, due to the pattern of the spread of cervical cancer. It tends to extend to the sidewall of the pelvis horizontally [37].

Radical vaginal trachelectomy

Radical vaginal trachelectomy (RVT) with laparoscopic lymphadenectomy is an alternative procedure for the preservation of fertility. It has gained worldwide acceptance as a method of surgically treatment of small invasive cervical cancers.

This procedure has been first described in 1994 by Daniel-Dargent *et al.* [38]. Since then over 1,000 cases have been reported to undergo a RVT and over 250 live births have been reported in women treated with this procedure [39, 40]. The success of this procedure is due to the strict criteria for patient selection. It has been estimated that about half of all women diagnosed with cervical cancer under the age of 40 are eligible for RVT [41-43].

Candidates for RVT

RVT includes the distal resection of the cervix, paracervical tissue, and upper vagina as in a Schauta vaginal hysterectomy (Table 1). The procedure of the resection of the tissue is the same as the distal part of a Wertheim's radical abdominal hysterectomy. Laparoscopically, a pelvic node dissection is performed.

Candidates suitable for RVT

1. Patients wishing to preserve their fertility,
2. Patients younger than 45 years,
3. Patients with cervical cancer Stage IA1, L1V0, IA2V0, IB1V0 according to FIGO. The tumour histological diagnosis should be referred as squamous cell or adenocarcinoma. Patients with neuroendocrine tumours are not suitable for RVT, because neuroendocrine tumours or small cell cancers of the cervix are more likely to be associated with lymph node metastases, lymphovascular space invasion (LVSI), and local and distant failure.
4. According to the MRI or colposcopy examination, cervical lesion less than two or 2.5 cm.

RVT was very beneficial in the 40% of patients who underwent this procedure, taking into consideration the above criteria. On the other hand, the probability of wrong patient's selection for RVT is about 10-12%. In this regard, it is possible that the patient will be treated with a definitive radical hysterectomy or adjuvant treatment as radiotherapy, due to extensive endocervical margins or lymphatic involvement [44]. The Outcomes following RVT for early stage cervical cancer are shown in Table 2.

Pre-operative assessment

Preoperative assessment must take into consideration several criteria, as the size of the tumour, the exact location and the distance of the isthmus and therefore the upper endometrial canal, as well as the probability of obtaining at least one cm of normal tissue surrounding the residual carcinoma.

An MRI in patients with pelvic mass can be useful [50], due to the importance of the accurate size and location of the mass, the severity of the endocervical involvement, the length of the cervical canal, and the distance between superior edges of the mass to isthmus [51].

The adequate clearance of the normal cervical stroma beyond the tumour is given by ensuring the exact length that the cervix is being rejected under this procedure.

Technique of RVT

1. In the beginning a laparoscopic pelvic lymph node dissection takes place [52, 53]. The pelvic side walls are exposed, external, internal, lower common iliac, and obturator lymph nodes are taken. Before proceeding to the vaginal part of the surgery, any suspicious nodes are collected and sent for a frozen section analysis. Infiltration of the paracervical and vaginal tissues using a 0.25% marcaine with one in 200,000 adrenaline is performed.
2. Preparatory phase: a two-cm cuff of the vagina is outlined with cutting diathermy.
3. Anterior phase: due to find dissection of cervix without any injury to bladder, vesicovaginal space in anterior of cervix and also paracervical spaces in both lateral sides determine the bladder pillars and ureters.
4. Posterior phase: determination of the pararectal space in order to clamp and cut sacral part and the ligament.
5. Lateral phase: assessing the ureters, the proximal part of parametria in the level of the isthmus is removed. The importance of the main uterus artery is salvaged, because it supplies the uterus circulation during pregnancy.
6. Cervix removal phase: one cm of isthmus is removed followed by endocervical curettage.
7. Cerclage phase.

Table 1. — Candidates For RVT [46-47].

Biopsy confirming cervical squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma
Patients < 40 years (some centers will allow women up to age 45)
Patients who want to preserve fertility
Patients with Stage IA1 with positive lymph-vascular space involvement
Stage IA2 - Stage IB1
Lesion size < 2cm or < 3cm with exophytic lesion
Adequate cervical length (> 2cm)
Consider imaging (MRI) to assess extent of lesion
Rule out distant mets with imaging prior to surgery
Must be performed 4 - 6 weeks following any cervical procedures (LEEP, cone)
Patient is a good candidate for surgery (healthy).

Table 2. — Outcomes following RVT for early stage cervical cancer.

Author (ref)	No. of patients	No of pregnancies	Outcomes Relapses/death
Shepherd <i>et al.</i> [45]	26	14 in 8	0/0
Dargent <i>et al.</i> [46]	82	22 in 18	3/2
Burnett <i>et al.</i> [47]	68	3 in 3	0/0
Plante <i>et al.</i> [48]	68	33 in 23	1/1
Bernadini <i>et al.</i> [49]	80	22 in 18	7/4

Recurrence risk factors

1. Size: lesions more than two cm [44, 54, 55]. The rate for recurrence probability is up to 29% in comparison with 1.6% for lesions less than two cm.
2. Lymphovascular invasion: the rate for lesions more than two cm is 12% compared to 2% for lesions less than two cm [55]. This rate is considered as exclusion criteria for RVT [56].
3. Pathologic type: although it is not clarified yet, nosquamous cell tumours are associated with higher recurrence. Also, neuroendocrine tumours are related with faster invasion and higher probability of recurrence, even with intact margin and no lymph node involvement [44, 55].

Complications in RVT

Some obstetrical complications associated with the surgery appear for women who undergo a RVT and subsequently have a pregnancy.

The risks of RVT during pregnancy include:

- Cervical incompetence
- Miscarriage
- Premature delivery
- Low birth weight

It should be mentioned that a loss rate up to 17% during the first trimester of pregnancy almost equals the loss rate of the general population, but in the second trimester the rate remains significantly high (up to 12%) [56].

Pregnancy-related outcomes after RVT (Table 3)

It is a high possibility that these patients, who are facing these complications, may require assistance of advanced reproductive technology to conceive [61].

Table 3. — Pregnancy-related outcomes after RVT.

Study	No of patients	No of patients attempted pregnancy	No of patients conceived (%)	Total pregnancies	Losses (%)	Pre-term (%)	Full-term (%)
Covens <i>et al.</i> [57]	32	13	4 (31)	5	2 (40)	0	3 (60)
Shepherd <i>et al.</i> [45]	26	13	8 (62)	14	5 (36)	7 (50)	2 (14)
Burnett <i>et al.</i> [47]	19	19	3 (16)	3	1 (33)	1 (33)	1 (33)
Schlaerth <i>et al.</i> [58]	10	10	4 (40)	4	2 (50)	1 (25)	1 (25)
Mathevet <i>et al.</i> [59]	95	43	34 (79)	56	22 (39)	5 (9)	29 (52)
Bernadini <i>et al.</i> [49]	80	39	18 (46)	22	4 (18)	6 (27)	12 (55)
Plante <i>et al.</i> [60]	72	31	31 (50)	50	10 (20)	8 (16)	28 (56)
Total	214	137	71 (52)	104	36 (35)	20 (19)	48 (46)

Conclusions

Nowadays, more and more women decide to become pregnant after the age of thirty. The screening tests' success has led to an increased detection of early stage cervical cancer. In order to preserve fertility, these women demand more conservative surgical techniques, such as RVT.

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Address reprint requests to:
I. BOUTAS, M.D.
Thessalonikis str 59, Kamatero
13451 Athens (Greece)
e- mail: ioannis.boutas@gmail.com