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Fertility Sparing Surgical Options in Early Stage Cervical Cancers

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Cervical cancer is the third most common genital cancer, accounting for about 2% of all new cancer cases and 2% of all deaths from cancer in 2014 [1].

Up to 42 percent of all cervical cancers are diagnosed in women before the age of 45, and with the advancements in cervical cancer screening, up to 40%of early cervical cancers are diagnosed in reproductive age women [2,3]. The excellent prognosis of early-stage cervical cancer is combined with the young age in many patients in whom a fertility-sparing surgery without compromising long term survival is of great importance. This approach should only be considered in women who have chance for successful treatment of their disease. Future reproductive and obstetrical risks, as well as long-term oncologic outcomes of the surgery, should also be discussed during counseling and decision-making.

Appropriate criteria to propose a fertility-sparing surgery are as follows [4]:

- A desire for future fertility
- A confirmed diagnosis of cervical cancer including histopathological types of squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma
- Tumor size less than 2 cm
- Stage IA1 disease with invasion to the lymph vascular space, stage IA2 disease or stage IB1 disease

- Tumors confined to the cervix as confirmed by preoperative pelvic Magnetic Resonance Imaging (MRI) or Positron Emission Tomography (PET-CT)
- No clinical evidence of metastases to the pelvic lymph nodes
- No previous documentation of infertility

A throughout preoperative assessment is mandatory to ensure that women have realistic expectations regarding fertility issues and satisfied obstetric outcomes, and the aim is to identify high-risk patients who are not eligible for a conservative oncological approach and to inform the patient and her family about the risks of immediate Radical Hysterectomy (RH) and/or need for postoperative adjuvant radiation or chemotherapy.

The first step in the assessment should be to take a biopsy, which offers basic prognostic information, notably contiguous type and lymphovascular involvement. If the result of the biopsy is neuroendocrine or small cell cancer, fertility-sparing procedures are not deemed proper, since they are associated with poor prognosis and a high risk of distant metastasis.

Site, extension and parametrial involvement of the tumors should be evaluated by clinical examination and radiologic imaging. MRI, which is the best preoperative imaging tool, allows precise and accurate evaluation of the the distance between the upper margin of the lesion and the isthmus [5]. The distance measurement is particularly important because in the cases in which this distance is less than 1 cm, Neoadjuvant Chemotherapy (NACT) followed by Radical Trachelectomy (RT) is preferred. Ultrasonography (US) can also be used to determine the dimensions of the tumor, amount of healthy cervical stroma, and a description of the parametrial involvement [6]. This is particularly helpful in cases with scarring/distortion of the cervix from the diagnostic procedure; however, interpretation of MRI can be challenging after a Loop Electrosurgical Excision Procedure (LEEP)/cone procedure [7]. On the basis of this information, in our study we used perioperative needle guided US, aiming to identify the correct incision plane to ensure the highest possibility of cure and tallest remaining cervical canal to maintain the reproductive functions as much as possible [8]. Assessment of lymph nodes involves Computed Tomography (CT), MRI and PET, which possess low precision in detecting lymph node metastatic disease [9,10].The most precise method to date is Sentinel Lymph Node Mapping (SLNM) during pelvic lymphadenectomy [9].

In peroperative assessment, the specimen is sent for frozen section if a visible lesion is present on clinical evaluation. The pathologist determines the distance between the upper endocervical tumor margin and the specimen excision margin. Ideally, 8 to 10 mm of normal tissue should be present; otherwise, an additional section of the cervix may require removal. If the tumor expands higher into the endocervical canal and the margins remain positive or too close (<5 mm), it may be necessary to perform a complete RH or definitive chemoradiation [11].

In the end, the type of the surgery that includes conization and trachelectomy is determined.

CONIZATION

Women with stage IA1 disease without Lymphovascular Space Invasion (LVSI) are suitible for treatment with cervical conization alone [12]. Since the risk for spreading of the lymph nodes, which is <1% remains quite minimal for patients with a stage IA-1 cancer in the absence of LVSI, conization of the cervix is a reasonable option for fertility-sparing treatment [13].

In IA1 with LVSI tumours, a combination of lymphadenectomy and cone biopsy is used because of increase in the risk of tumor recurrence from 3.2%to 9.7% [14-16].

In IA2 tumours, usually Radical Vaginal Trachelectomy (RVT) with pelvic lymphadenectomy is performed; however, in selected patients whose margin is negative, cone biopsy or Simple Trachelectomy (ST) combined with lymphadenectomy is prefered [17]. In stage IA2 tumors, pelvic lymph node dissection must be added to conization, because lymph node metastases increase by 5-8 % in these cases [18].

Morbidity—Conization that causes less injury and bleeding compared to hysterectomy and Radical Trachelectomy (RT), ensures a better quality of life [19].

Recurrence—Conization appears safe in IA1 stage, as no difference has been reported in survival rates between this approach and hysterectomy. In a recent study of 1,409 patients, the survival rate after a 5-year follow-up was 99% following hysterectomy and 98% following conization. Recurrence rate was 3% [20]. In a study with 22 patients having stage IA2 and IB1 (with tumor diameter <20 mm) 5-year Disease-Free (DF), and Overall Survival (OS) rates were 85.9% and 93.7%, respectively [21]. In another two studies, the reccurence rate at stage IB1 (with tumor diameter <25 mm) was 3-5% [22,23].

Reproductive outcomes—Fagotti A et al. reported that 5 of 17 patients, tried to conceive and two of them two obtained the achieved natural pregnancy while *in vitro* Fertilization (IVF) was unsuccessful in the remaining three cases, showing the absence of correlation with any cervical factor of infertility. In that study, pregnancy rate was 40% [24], similar to that reported by Maneo et al [25].

Pregnancy outcome—Two meta-analyses evaluated the obstetric outcome after conization [26,27]. Both studies reported an increased preterm delivery Relative Risk (RR) 2.59; 2.78 and low birth weight RR 2.53; 2.86 in patients with a history of conization. However, the recent studies seem to be more promising. Ditto et al. reported the pregnancy rate as 53%, term pregnancy as 27%, and live children as 28% for stages IA2 and IB1 disease [21]. Maneo et al. reported pregnancy rate as 47%, live birth rate as 39%, and 3 preterm deliveries with the earliest gestation at 27 weeks for stage IB1 disease with tumor diameter <25 mm [22]. Lindsay et al. studied 43 patient, 37 of them were IB1 and the pregnancy rate was found as 42%, live birth rate 35% and preterm deliveries 9.3% with the earliest gestation at 32 weeks [23]. According to Biliatis's study,

there were no preterm deliveries or second trimester losses after treatment of stage 1B1 disease. Among 35 patients, seven pregnancies have been reported, with a live birth rate of 100% [28].

In conclusion, the efficacies of laser conization, LEEP, and cold-knife conization are similar [29]. There is no major difference in obstetrical outcome among the three techniques [30].

SIMPLE TRACHELECTOMY

Reportedly, patients with tumours less than 2 cm in diameter and negative pelvic lymph nodes carry minimal risk of parametrial involvement, making a wide resection of parametrium unnecessary. Therefore, in these cases a ST procedure combined with pelvic lymphadenectomy is the only required [31-35].

Reccurence—Out of 6 series of ST/cone for the treatment of early cervical cancers, only 2 (1.0%) recurrences have been reported in total 189 cases, but 9% of patients required adjuvant treatment after ST/cone, mostly for positive endocervical margins or lymph node metastasis. Most underwent a definitive radical hysterectomy [22,26,28,36-39].

Pregnancy outcomes—According to the literature, the pregnancy outcomes after ST are similar to that of post radical trachelecyomy. The pregnancies ended with a term delivery, a preterm delivery, and second trimester loss are 61%, 17% and 7%, retrospectively [40-42], which therefore should be considered as high-risk pregnancies.

RADICAL TRACHELECTOMY

In combination with a laparoscopic pelvic lymphadenectomy, RT is the most common and accepted fertility-sparing procedure for early cervical cancer [43]. RT is ideal for Stage IA1 cervical cancers with LVSI, stage IA2 cancers, and stage IB1 cancers less than 2 cm [44]. The procedure includes removal of the cervix, parametrium and upper vagina. Prior to the surgery, a complete laparoscopic lymph node dissection is performed to exclude the presence of lymph node metastasis. During peroperative frozen section, RT is aborted if pelvic lymph nodes or paracervical tissue are found to be tumor involved, and lymphadenectomy is completed at the pelvic and para-aortic area followed by primary chemoradiation. If a permanent section confirms tumor-involved resection margins or endocervical tumor-free margin less than 5 mm or a tumor diameter more than 20 mm, then RH or primary chemoradiation must be performed [45,46]. RVT, which was first described by Daniel Dargent in 1994 [43], is the most used surgical procedure which can be performed by either abdominal or Minimally Invasive Surgery (MIS).

Abdominal Radical Trachelectomy (ART) allows for a more extensive parametrial resection. Therefore, it is prefered in lesions larger than 2 cm, in which more radical surgery is needed [47]. It is advantageous in patients with distorted vaginal anatomy, in pediatric patients, and in bulky exophytic lesions [48]. But because of wider parametrial resection, ligation of uterin arteries may increase the risk of endometrial atrophy, cervical stenosis, and adverse pregnancy outcome

such as low birth weight [49]. Recent improvments in the surgical technique that permit preservation of the uterine artery are expected to decrease early and late term consequences. Moreover, new advances in the surgical technique enable nerve-sparing radical trachelectomy in hopes of reducing the morbidity of the procedure due to urinary complication.

Minimally invasive approaches in RT are now emerging in the gynecological oncology literature, which differ from the classical surgery only in the access route used. They also reduce postoperative pain and intraoperative blood loss, shorten recovery, and offer better cosmetic results [50-52].

Laparoscopic Radical Trachelectomy (LRT) is, in principle, identical to the ART and with its similar radicality, it has all advantages of an abdominal approach combined with the minimally invasive surgery.

Robotic Radical Trachelectomy (RRT) offers excellent visualization of the vasculature and parametrial tissues, which should be isolated during this procedure [53]. However, one group reported a high rate of conversion to RH in view of inadequate clearing of the endocervical surgical margin, possibly because of difficulty palpating or feeling precisely the lower uterine segment, thus making it more difficult to determine where to amputate the cervix in relation to the level of the tumor [54].

Morbidity—The typical complications reported in patients undergoing RT include dysmenorrhea, dysplastic Pap smears, irregular or intermenstrual bleeding, problems with cerclage sutures, excessive vaginal discharge, amenorrhea and cervical stenosis regardless the surgical type [55]. Another potential complication unique to this procedure is occasional reports of deep dyspareunia, which occurs because the uterus and the ovaries are much lower in the pelvis and accompanied by cervical stenosis [56].

Complication rate is 4% to 6% in VRT, similar to laparoscopic-assisted RH [45,46,57-59]. In one of the largest series, the perioperative morbidity of VRT (n=118) was compared with that of vaginal radical hysterectomy (VRH) (n=139). The rates of intraoperative complications were found as 2.5 and 5.8% and postoperative complications 21.2 and 19.4%, respectively [45]. In a study comparing VRT with ART, the overall complication rate was not significantly different in the two groups [60].

In ART, complications are usually related to abdominal approach itself. Overall, complication rates seem to be similar to those of abdominal radical hysterectomy and are not different from VRT [58,61]. Most of the studies reviewed did not show perioperative complications [62,63]. However, in 392 ARTs performed, the most frequently reported intraoperative complication was blood transfusion (10 cases) [54,64,65] ; while the most frequent postoperative complication was cervical stenosis [54,62- 64,66].

As for LRT, the intraoperative complications vary from 2% to 9% [67-73]. In a large study

of 170 patients, 14 severe perioperative complications (8.2%) occurred of which 5 required conversions to open surgery; the most frequently seen complications were bowel injuries and hemorrhages, and 1intolerance the Trendelenburg position was developed, which is peculiar to laparoscopic surgery [74].

In literature, the number of RRT patients is much too limited. The fact that we have less knowledge about it is due to scarce data. In a study, out of 6 patients undergone the procedure, 2 had postoperative complications: One had port site herniation, and the other, hematoma [75]. Nick et al. compared open (n=25) versus robotic (n=12) RTs [54]. There were no intraoperative complications with both surgical modalities. Although there was no significant difference in the rate of individual morbidities between surgical modalities, rate of late morbidity was higher in morbidity in the open RT group compared to the RRT group with 58% vs. 13%. Because robotic surgery is a relatively new procedure, it is too early to compare it with other surgical approches in terms of morbidity and, oncologic and reproductive outcomes.

Recurrence—After VRT, the overall rate of cervical cancer recurrence is comparable with those following RH in the lesions with similar sizes [45,76]. A review of data from 924 patients from six series of cervical cancer treated by VRT showed the rate of recurrence and mortality as rates: recurrence 4.4% and 2.1%, respectively [77]. In a case-control study, 137 women undergone VRT were matched with RH controls. Five-year recurrence-free survival rates were similar between groups (95 and 100%) [78].

Data on over 330 ARTs exhibited excellent oncologic outcome, with recurrence rate <4% [77]. The safety of ART has been recently reviewed in 485 patients from 29 articles, and only 3.8% of the patients experienced a recurrence and 0.4% died after a median follow-up of 31.6 months [61]. A Hungarian group described 5-year survival rate of patiens with cervical cancer IB1 and IB2 after ART as 93.5% at median 90 months follow-up [79].

The survival rate in different laparoscopic studies is consistent with other laparotomy studies [80,81]. In LRT, 5-year survival rate changes between 90.5%-100% and the recurrence rate between 2.8%-6% [67-71]. According to a recent study, in stage IA2- IIB, the 5-year OS was found as 94.1%, specific survival 94.3%, and DFS 88.8% [74]. Given that the tumor size is the major predictive factor for an adverse outcome when comparing VRT, ART, LRT for tumor size less than 2cm, the respective recurrence rates were found 2.9%, 2.4% and 6% for tumor size greater than 2cm, and the recurrence rate as 20.8%, 20%, and 20.7% respectively [42,82] .

Published evidence on oncological safety of robotic surgery is not so significant due to small cohort size or limited follow-up time. In a series of 6 and 4 patients there was no recurrence at the median follow-up periods of 11 and 3 months, respectively [75,83]. Hoogendam's study reported a recurrence rate of 13% at the median follow-up of 29.5 months. The overall 5-year progression free and disease specific survival were found as 81.4% and 88.7%, respectively. For stage IB1, these rates were 80.5% and 87.9%. In this study, lymp node negative patients had an excellent

prognosis of a 95.0% 5-year survival, which is similar to larger studies of open surgery [84]. In Nick's study, there was no reccurence in both open and robotic trachelectomy groups, but the median time of follow-up was significantly shorter in the robotic group (10.8 months vs. 26.4 months) [54]. Similarly, Vieira MA et al. compared open (n=58) versus minimally invasive surgery (MIS=laparoscopic or robotic) in RT (n=42). Median follow-up was shorter in the MIS group compared with the open surgery group (25 months vs. 66months) and there was one recurrence in the laparotomy group, while no recurrence was observed in the MIS group [85].

Reproductive outcomes—Infertility has been reported in 25–30% of patients after trachelectomy, and possible causes include cervical cervical stenosis, decreased cervical mucus, and subclinical salpingitis [57,86]. Cervical factors (eg, cervical stenosis) are accounted for 40 to 75% of infertility, and the remaining are due to causes unrelated to the surgery [40,87-89]. Fertility and obstetrical outcomes related to vaginal and laparotomic approach are widely documented, while more investigations are required about minimally invasive surgery.

The overall pregnancy rate is 30% for VRT and 15% for ART [90]. For ST, the pregnancy rate is about 50% [42]. In the 355 RT procedures, which include VRT and ART, the majority of the patients obtained to concive by 70% [86]. In a series of 105 patients undergone VRT, ART and RRT; 23 (66%) of 35 women who attempted to conceive after radical trachelectomy were successful. Out of the 23 women who delivered, 83% had 1 pregnancy and 17% 2 pregnancies. Out of 23 women who became pregnant, 12 (52%) conceived spontaneously, while 11 (48%) conceived with assisted reproductive technologies [91].

It was observed in several investigations that pregnancy rates in VRT were >50%, and live birth rates varied from 50 to 72% [46,59,92,93]. Sonoda et al. reported a 79% pregnancy rate occurring in 36% of these after assisted reproductive techniques [94]. Live birth rate was 100%. Bernardini et al. showed a 56.4% pregnancy rate with a 82% live birth rate [87].

In one study including 116 patients using ART, 10 pregnancies with 6 live births were reported [92]. In different series, pregnancy rates differed between 3.6 and 100% [64-66,95,96], which seems quite confusing. The live birth rate ranged between 50-100%. The best obstetrical outcome reported so far was a pregnancy rate of 74% [97].

The reproductive outcome of patients after LRT appears to be similar to those who underwent vaginal or abdominal RT. In one of the largest studies on reproductive outcomes after LRT with 55 patients, 18 patients (32.7%) attempted to conceive after LRT, and 10 patients succeeded in 14 pregnancies. Six of 18 patients received fertility treatments, resulting in 5 pregnancies and 9 natural pregnancies. Pregnancy and live birth rates after LRT were 55.6% and 71.4%, respectively [98]. In another study with 56 patients, 25 women attempted to conceive, of whom 13 succeeded for a total of 21 pregnancies, resulting in a pregnancy rate of 52%. Ten of these21 pregnancies were the result of assisted reproductive technologies [99].

As for RRT, two studies performed by Nick et al. and Burnett et al. did not report pregnancies

[54,75]. In Nick's series, 23% of women experienced postoperative infertility, a rate comparable to that published in the largest series of pregnancy outcomes following RT [78]. Up to date, a total of 36 RRTs have been published in the literature, with 4 spontaneous pregnancies [54,75,85,100,101]. Two of them delivered after week 35 and the remaining two had ongoing pregnancies when this article was released.

Pregnancy outcomes—The first trimester miscarriage rate is comparable to that of the general population (17%); however, the rate of second trimester is on average two fold higher compared to the general population (8.6%) [40,41,91,102-104].

Premature labour before the 32nd week and between the 32nd and 37th week of pregnancy has been observed in approximately 12% and 28% in VRT and ART, respectively [90]. The shortening of the cervix plays an important role in the risk of premature delivery here as proven in patients after cone biopsy (RR about 2) [105]. A literature review including 200 pregnancies reported that 66% of pregnancies following RT ended in a live birth [106]. Overall, 42% of the pregnancies resulted in the birth of a healthy newborn at term; 25% of the pregnancies ended in preterm delivery before 37 weeks of gestation, but there was significant prematurity in only about one-half of these deliveries before 32 weeks.

A literature review of 452 pregnancies post-VRT reported that 60 to 75% of pregnancies reached the third trimester, and of those, two-thirds delivered at term, with <10% delivering with severe prematurity (<32 weeks) [77].

Recent data regarding ART have displayed a total of 101 cases with 31 pregnancies , 10% first trimester miscarriages, 19% second trimester losses, and 52% third trimester deliveries [97]. In another study, the pregnancy rate was reported as 36.2%. Among 31 pregnancies, 4 patients had first trimester miscarriage and 1 had second trimester miscarriage. Four patients had a preterm birth in the second trimester and 17 patients delivered in the third trimester. Out of the 17 pregnancies that reached the third trimester, 11.8% was preterm births before 32 weeks, 64.7% delivered between 32 and 37 weeks and 23.5% at ≥37 weeks of gestation [107].

In a study investigating obstetric outcomes of 21 pregnancies after LRT, 5 resulted in first trimester miscarriages, 2 in second trimester miscarriages, and 13 in live births. Ten pregnancies reached the third trimester, of which 3 were delivered > 37 weeks [99]. The preterm birth rate of patients who gave birth after a vaginal or abdominal radical trachelectomy was 24.7% and 38.7%, respectively [61,77]. However, the preterm birth rate after LRT was 60% in Park's study, in which, nevertheless, four of six preterm deliveries were at 36 weeks of gestational age and only two preterm deliveries were at 28 weeks of gestational age [98].

The largest comparative series of open vs. MIS of RT showed that the pregnancy rate was higher in the open surgery group compared to the MIS group (51% vs. 28%) [85]. In the open surgery group, the rates of first trimester miscarriage was found as 18.8%, second trimester

deliveries 6.2%, third trimester deliveries 56.2%, and term delivery 6.2%; while in the MIS group the rates of first trimester miscarriage was found as 33.3%, second trimester deliveries 0.0%, third trimester deliveries 33.3% and term delivery 0.0%.

There is no consensus on application of cervical cerclage. Some centers prefer to place a preventive cerclage during oncological surgery, while others prefer placement during pregnancy [62,65,95]. There is also no consensus about timing of the attempt to conceive, but a period of minimum 3 months seems to be reasonable. In the patient's undergone fertility-sparing surgery, pregnancy is ceased by cesarean section at 37 to 38 weeks of gestation, because in vaginal delivery, a probable lateral cervical tear in the short scarred cervix is more likely to extend into the uterine vessels [47].

Neoadjuvant Chemotherapy—A new approach, NACT is used to chemo-reduce size of the lesion, making it possible to perform fertility sparing surgery in Stage FIGO IB1 >2 cm to IIA1 [25,108-110]. The aim is not only to offer a greater chance of fertility preservation, but also to provide a better obstetrical outcome. In 5 series of NACT, followed by fertility-preserving surgery performed in 77 cases, optimal response was 71% and reoccurrence rate 7.2%. Fertility was preserved in up to 80% of the cases. Thirty five pregnancies have occurred in 28 women who attempted to conceive with 11 preterm (31%) and 13 term (37%) delivery [111].

Follow-up—There are no definitive guidelines for follow-up of patients after RT. A colposcopic examination and cervical cytology are performed every three to four months for the first three years, every six months for the next two years and yearly thereafter. Also, pelvic MRI at 6, 12, and 24 months is recommended [112].

Fertility-preserving options should not be taken as a standard treatment. The risk and benefits related to each treatment modality should be evaluated with a multidisciplinary approach.

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