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Minimally invasive radical trachelectomy: Considerations on surgical approach

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A B S T R A C T

Current evidence supports that radical trachelectomy is a safe and feasible alternative to patients with early-stage cervical cancer who wish to preserve fertility. In addition, published retrospective literature supports that oncologic outcomes are equivalent to those of radical hysterectomy. First published as a vaginal approach, a number of other approaches have been reported including laparotomic, laparoscopic, and robotic. In 2018, the first ever prospective randomized trial (LACC) comparing open vs. minimally invasive radical hysterectomy showed worse disease-free and overall survival for the minimally invasive (both laparoscopic and robotic) approach than the open approach. This landmark publication raised concerns regarding the oncologic safety of minimally invasive radical trachelectomy.

In the United States, minimally invasive became the dominant approach by 2011 for radical trachelectomy. Given that radical trachelectomy is an infrequent performed procedure, only small retrospective studies, systematic reviews, and large database studies have been published. These studies are limited by their retrospective nature, small sample size, patient selection bias, unbalanced groups, and sequential surgical approach comparisons. However, the available evidence thus far shows that oncologic outcomes for both open and minimally invasive radical trachelectomy are equivalent.

Given the rarity of the procedure and the low recurrence and death rates of patients with early-stage cervical cancer undergoing radical trachelectomy, a prospective randomized trial seems

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unlikely. A multi-institutional international registry study (International Radical Trachelectomy Assessment – IRTA – study) has been recently completed evaluating open vs. minimally invasive radical trachelectomy. There are three ongoing prospective studies evaluating the possibility of less radical surgery in a low-risk early-stage cervical cancer population, ConCerv, SHAPE, and GOG 278. We look forward to the final results of these studies that will hopefully shed light on the optimal treatment option for patients with early-stage cervical cancer wishing to preserve fertility. This article will review the most impacting publications comparing open vs. minimally invasive radical trachelectomy and analyze the limitations of the current available literature.

Introduction

Cervical cancer is the fourth most common cancer in women worldwide [1]. It is frequently diagnosed at reproductive age, with 37% of new cervical cancers diagnosed under the age of 45 [2]. In the United States, almost 44% of women with cervical cancer are diagnosed at an early stage. Due to a delay in childbearing, an increasing number of reproductive-aged women diagnosed with cervical cancer desire fertility-sparing treatment.

Vaginal radical trachelectomy, first performed in 1986 and reported in 1994 by Dargent et al. [3], was the first option for fertility preservation in young patients with early-stage cervical cancer. Single institution [4,5], reviews [6], and national cancer database studies [7] have described similar recurrence rates, morbidity, and mortality compared to the standard radical hysterectomy. These publications have led to the conclusion that radical trachelectomy is a viable fertility-sparing option for early-stage cervical cancer patients. The rates of radical trachelectomy have increased in the past decades. In the United States, trachelectomy rates increased from 1.5% in 2004 to 3.8% by 2014 ($p < 0.001$) with the greatest increase seen in women <30 years of age (4.6% in 2004 to 17.0% in 2014, $p < 0.001$) [7].

Since its first publication as a vaginal procedure, the approach to radical trachelectomy has been reported via laparotomy (1997), laparoscopy (2003), and the robotic routes (2008). A recent systematic review by Smith et al. [8] included a total of 2566 patients who underwent radical trachelectomy from 1999 to 2019 through vaginal, laparotomic, or laparoscopic approach. Not surprisingly, due to the time of publication, 58.1%, 37.2%, and 4.7% of the included cases were performed using vaginal, abdominal, and laparoscopic approaches, respectively. Overall, the median tumor size was 1.5 cm. Tumor size ≤2 cm accounted for 69.2% and tumors larger than 2 cm for 30.8% of all cases with a median depth of stromal invasion of 5 mm (range, 3–12). Most patients had FIGO 2009 stage IB1 tumors (74.8%) followed by IA2 (15.5%). Approximately one-third of tumors had lymphovascular space invasion (31.2%), and 6.1% (112/1835) had pelvic lymph node involvement. With a median follow-up of 48 months (range, 2–202) across studies, the median recurrence rate was 3.3% (range, 0–25); the median time to recurrence was 26 months (range, 8–44). Median 5-year recurrence-free and overall survivals were 94.6% (range, 88–97.3) and 97.4% (range, 95–99), respectively. The post trachelectomy pregnancy rate was 23.9%, with a live-birth rate of 75.1%.

The vaginal approach has the advantage of a faster recovery and return to daily activities with the disadvantage of requiring training in complex vaginal surgery. The reported rate of intraoperative conversion to hysterectomy is 3.9% and the rate of adjuvant therapy is 4.4%. With a follow-up time of 50.9 months (range, 9.8–202) the recurrence rate is 3.8% (0–9.9), median 5-year recurrence-free survival 94.4% (range, 88–97.3), death rate 1.7 (range, 0–3), and median 5-year overall survival 97.4% (range, 95–99) [8].

The laparotomic or open approach was reported in a subsequent publication in the literature in 1997 [9]. Of note, the first abdominal radical trachelectomy was published by Eugen Bogdan Aburel in

1957; however, often not credited as none of the patients became pregnant. The laparotomy route has the advantage of not requiring specific training in complex vaginal surgery. Moreover, it became the approach of choice in patients with larger tumors as it allows for larger parametrium resection than its vaginal counterpart [10]. As a disadvantage, the open approach has higher estimated blood loss and transfusion rates, with longer hospital stay than the vaginal surgery. For the open approach, the reported rate of intraoperative conversion to hysterectomy is 12.6% with 5.4% of patients receiving adjuvant therapy. With a median follow-up time of 38 months (range, 2–66), the recurrence rate is 3.3% (0–9.8), the 5-year recurrence-free survival 96.3%, the death rate 1.5 (range, 0–1.7), and a 5-year overall survival 98.6% [8].

In 2003, laparoscopic [11] and in 2008, robotic [12,13] radical trachelectomy were published offering the perioperative advantages already known for minimally invasive surgery (MIS) such as less blood loss, lower transfusion rates, shorter length of hospital stays, and faster return to daily activities. All publications on MIS are retrospective case series with small sample size and short follow-up time when compared to the vaginal and open radical trachelectomy. In the study by Smith et al. for the laparoscopic approach, the rate of intraoperative conversion to hysterectomy is 11.8% with no patients receiving adjuvant therapy. With a follow-up time of 25 months (range, 3.5–52.8) the median recurrence rate was 0% (0-25), the 5-year recurrence-free survival was not reported, death rate was 0% (range, 0–3.7), and the 5-year overall survival was not reported [8].

In 2018, a randomized prospective trial (LACC) comparing open vs. minimally invasive radical hysterectomy showed worse oncologic outcomes for the MIS group with a worse disease-free survival and overall survival [14]. This lead many to question the safety of minimally invasive radical trachelectomy, given that the fertility-sparing procedure routinely includes similar patient population as those included in the LACC trial.

In this chapter, we will review single institutions, systematic reviews, National Cancer Database, and international collaboration study reporting on the oncologic outcomes of open and minimally invasive approach for radical trachelectomy. Furthermore, we will evaluate the possibility of less radical surgery as a fertility-sparing option updating on three ongoing prospective studies.

Surgical approaches

Open radical trachelectomy

A recently published single-institution retrospective study by Li et al. [15] is the largest series on open radical trachelectomy published to date. The study included 333 patients with FIGO 2009 stage IA1 with LVSI – IB1 cervical cancer who underwent open radical trachelectomy from 2004 to 2017. The most common histology was squamous carcinoma 271 (81.4%) and stage IB1 255 (76.6%). One hundred thirty-two women (39.6%) had tumors $\geq$2 cm. With a median follow-up of 56 months (range, 6–169), 11 patients (3.3%) had a recurrence, and five patients (1.5%) died of the disease. The cumulative 5-year recurrence-free survival and overall survival rates were 96.3 and 98.6%, respectively. Recurrence rate in women with tumors $\geq$2 cm was comparable to that in patients with tumors <2 cm (5.3% vs. 2.0%, respectively, p = NS). The study showed a significantly higher recurrence rate for patients with adenosquamous carcinoma than for squamous or adenocarcinomas (18.2%, 3.9%, and 2.6%, respectively, $p < 0.05$). All patients with adenosquamous carcinomas that recurred had tumors $\geq$2 cm. On multivariate analysis, the only independent risk factor for recurrence was histology type. The authors concluded that the survival rate following open radical trachelectomy was favorable and a safe option for well-selected patients with stage IB1 cervical cancers $\geq$2 cm. However, for adenosquamous histology and tumor size $\geq$2 cm caution was advised when contemplating the open approach.

Minimally invasive radical trachelectomy

With the advantages over the open approach with regard to perioperative outcomes, comparable to the vaginal approach, MIS gained popularity for advanced pelvic surgery in gynecologic oncology worldwide. Moreover, as surgeons were more familiar with this approach, as opposed to the vaginal route, minimally invasive radical trachelectomy became a routine approach for this complex surgery.

The first laparoscopic abdominal radical trachelectomy was reported by Lee and colleagues in 2003 [11] and later, in 2008, the first publications on robotic radical trachelectomy were published [12,13]. Thus far, oncologic outcomes as published in small retrospective series and systematic reviews have suggested that the minimally invasive approach may be equivalent to its open counterpart. However, one should note that when evaluating the literature on MIS, studies are limited by the fact that in comparison to other studies, particularly those evaluating the vaginal or open radical trachelectomy, the follow-up time is shorter in the MIS groups; thus, events for recurrence might not have manifested at the time of publication. In addition, given the time trend of publication, many of these studies that provide comparative data with the vaginal or open approaches are not concurrent comparisons but rather sequential comparisons.

The first series comparing robotic to open radical trachelectomy was published in 2012 and included 37 patients (open, 25; robotic, 12) [16]. Patients undergoing robotic radical trachelectomy had significantly less blood loss (62.5 mL vs. 300 mL, $p = 0.0001$) and decreased length of postoperative stay (1 vs. 4 days, $p < 0.001$), with no difference in operative time. Twenty-three patients (62%) had no residual cervical disease on final pathology. Five (open, 1; robotic, 4) underwent conversion to radical hysterectomy secondary to close (<5 mm) endocervical margin ($p = 0.08$). Acknowledging a shorter median time of follow-up among patients in the robotic group (10.8 months [range, 0.43–24.6] vs. 26.4 months [0.30–64.9]; $p = 0.004$) no recurrences were reported for either approach. In 2015, Vieira et al. [17] published a retrospective study comparing 100 patients (open, 58; MIS, 42 [robotic or laparoscopic]) from three institutions who underwent radical trachelectomy from 2002 to 2013. Both approaches were compared in terms of perioperative, oncologic, and pregnancy outcomes. Both groups were similar in terms of age, body mass index, histology, lymph vascular space invasion, and stage ($p > 0.05$). Median surgical time was 272 min [range, 130–441] and 270 min [range, 150–373] for MIS and open, respectively ($p = 0.78$). Blood loss was significantly lower for MIS vs. laparotomy (50 mL [range, 10–225 mL] vs. 300 mL [50–1100 mL]) ($p < 0.0001$). The length of hospitalization was shorter for MIS than for laparotomy (1 day [1–3] vs. 4 days [1–9], $p < 0.0001$). Among 83 patients who preserved their fertility (MIS, 33; open, 50), 34 (41%) patients attempted to get pregnant. Sixteen (47%) patients were able to do so (MIS, 2 vs. laparotomy, 14, $p = 0.01$). The pregnancy rate was higher in the open surgery group than in the MIS group (51% vs. 28%, $p = 0.018$). Median follow-up was shorter in the MIS group than in the open surgery group (25 months [range, 10–69] vs. 66 months [range, 11–147]). At the time of publication, there was one recurrence in the laparotomy group and none in the MIS group with no deaths from disease reported for either group.

In 2016, Murat et al. [18] published a review comparing radical trachelectomy performed by both minimally invasive approaches (robotic, 45; laparoscopic, 216). Groups were different in terms of histology with a higher prevalence of adenocarcinoma in the robotic group (63% vs. 21%; $p < 0.001$) and more patients having stage IB1 in the laparoscopic group (84% vs. 47%; $p < 0.001$). With a mean follow-up time of 8 months (SD 7.5) in the robotic and 34 months (SD 20) in the laparoscopic group ($p < 0.001$), 13 patients who underwent laparoscopic surgery had a recurrence with no recurrences in the robotic group. Of note, in this article the authors provide no information regarding tumor size and correlation with disease recurrence.

A systematic review published in 2016 by Bentivegna et al. [19] reported oncologic outcomes of six fertility-sparing procedures (conization or simple trachelectomy, neoadjuvant chemotherapy followed by fertility-sparing surgery, radical trachelectomy via vaginal, open, laparoscopic, or robotic approach). A total of 28 series including 660 patients who underwent open surgery were included in the review. The recurrence rate for the open approach was 5% with 9 deaths reported. Laparoscopic radical trachelectomies were reported in 18 series including 238 patients. With a median follow-up of 24 months (range, 4–66) the recurrence rate in the laparoscopic group was 6%. For the robotic approach, 89 patients were reported in nine series. Among patients with FIGO 2009 stage IB1 disease, 20% had close or positive margins. Only one series reported follow-up time, which was longer than 34 months, and four series did not report any follow-up suggesting that robotic radical trachelectomy was still in the feasibility stage. In this review, there were no perioperative or oncologic outcomes comparisons among surgical approaches as it is a systematic review, not a meta-analysis.

In 2018, a National Cancer Database study was published to assess the trends in the use of trachelectomy in the United States and to examine the outcomes of the procedure compared with

hysterectomy in <50 years of age women with FIGO 2009 stage IA2–IB2 cervical cancer [7]. A total of 15,150 patients (hysterectomy, 14,714; trachelectomy 436) who underwent surgery from 2004 to 2014 were included. During the study period, trachelectomy rates increased from 1.5% to 3.8% ($p < 0.001$) with the greatest increase seen in women >30 years of age (4.6% in 2004 to 17.0% in 2014, $p < 0.001$). After propensity score matching, there was no association between trachelectomy and the risk of mortality (hazard ratio 1.24, 95% CI 0.70–2.22). Mortality rate was 6.0% for hysterectomy vs. 5.2% for trachelectomy. Similarly, 5-year survival rates were similar between trachelectomy and hysterectomy for all stages examined, 92.4% (95% CI 89.7–94.4) and 92.3% (95% CI 88.5–94.9), $p = 0.70$, respectively. The authors concluded that the use of trachelectomy for early-stage cervical cancer has increased in the United States, particularly in young women (<30 years of age) with similar survival rates for trachelectomy and hysterectomy.

Impact of LACC trial

A recent multicenter, prospective, randomized trial (LACC Trial) including patients with FIGO 2009 stage IA1 with lymphovascular space invasion-IB1 cervical cancer who underwent radical hysterectomy via open vs. minimally invasive approach (laparoscopic or robotic) showed 4.5-year disease-free survival of 86% for minimally invasive radical hysterectomy and 96.5% for the open approach. MIS was also associated with higher rates of loco-regional recurrences [HR: 4.26 (95% CI 1.44–12.6), $p = 0.009$] and a higher risk of death [HR: 6.00 (95% CI 1.77–20.3), $p = 0.004$] [14]. Several retrospectives and national database studies have subsequently shown similar results as the LACC trial [20–24]. Moreover, secondary objectives from the LACC trial were published showing no difference between the open and MIS in terms of perioperative complications rate or quality of life outcomes [25]. The unanticipated results of the LACC trial raised concern regarding the oncologic safety of minimally invasive radical trachelectomy.

After the publication of the LACC Trial, a National Cancer Database study including 246 patients aged <50 years, with early-stage cervical cancer who underwent open ($n = 102$) vs. minimally invasive ($n = 144$) radical trachelectomy between 2010 and 2015 was published [26]. The primary objective of the study was to evaluate the trends of minimally invasive radical trachelectomy in the United States. The study showed a significant increase in the use of minimally invasive trachelectomy from 29.3% in 2010 to 75.0% in 2015 ($p < 0.001$), with MIS becoming the dominant approach for trachelectomy by 2011 (54.8%). Although oncologic outcomes were not the primary endpoint of the study, as a secondary observation, the 4-year overall survival rates were 95.7% (95% CI, 88.7–98.4) for the MIS and 92.3% (95% CI, 83.5–96.5) for the open group. With a median follow-up time of 37 months (interquartile range, 23–51) for the MIS and 40 months (interquartile range, 26–67) for the open approach group, there were 11 (5.3%) deaths [MIS, 4 (3.5%); open, 7 (7.6%), $p = 0.25$]. The authors concluded that MIS has become the dominant modality for radical trachelectomy in reproductive-aged women with FIGO 2009 stage IA2-IB cervical cancer after the year 2011 and that survival of these patients who underwent radical trachelectomy is favorable regardless of surgical modality. Although the study showed no difference in survival between the MIS and laparotomy approaches, the effects of minimally invasive on survival remain unknown and further study is warranted.

Given the limited number of patients who are candidates for radical trachelectomy and the low recurrence rate, a randomized control trial comparing open to minimally invasive approaches is unlikely. As a result, there is an international, retrospective study evaluating open vs. minimally invasive (laparoscopic or robotic) radical trachelectomy in patients with preoperative tumors $\leq$2 cm. The aim of the study, International Radical Trachelectomy Assessment (IRTA), is to compare 4.5-year disease-free survival of patients with early-stage cervical cancer who underwent open vs. minimally invasive radical trachelectomy [27]. Inclusion criteria comprised patients with early-stage (FIGO 2009 IA2-IB1) cervical cancer with tumors $\leq$2 cm, squamous, adenocarcinoma, and adenosquamous carcinomas that underwent radical trachelectomy via open vs. MIS approach between January 2005 and December 2017. A total of 646 patients (open, 358; MIS, 288) from 18 sites across 12 countries were included in the analysis. The preliminary results of this study were presented at the 2019 Annual Global Meeting of the International Gynecologic Cancer Society (IGCS) held in Rio de Janeiro, the investigators found no difference in disease-free survival when comparing patients who underwent open vs. minimally

invasive radical trachelectomy. However, patients in the open surgery group had more high-risk features for recurrence. The results of this study are highly anticipated as it may shed light on the oncologic safety of minimally invasive radical trachelectomy in comparison to the open approach.

Published studies limitations

There are several limitations of the published literature as it pertains to the comparison of open vs. MIS radical trachelectomy. One of the consistent flaws lies in the fact that all studies are retrospective in nature and sample sizes are very small. Therefore, none of the studies has enough power to identify a significant difference between open and MIS. In other words, none have enough events to declare a power of 80% and significance level of 0.05. Although the conclusions routinely suggest that minimally invasive radical trachelectomy is associated with the same oncologic outcomes (recurrence and death) as the open approach, as p values are >0.05, one should keep in mind that the absence of statistical significance does not mean that both approaches are equivalent but possibly a consequence of a small sample size.

Another limitation of these studies is the use of historical controls. In other words, surgeries performed by both approaches were not concurrent, but rather sequential. As for other diseases, cervical cancer staging, diagnostic images, adjuvant treatment, and recommendation guidelines have changed over time. First, the use of cross-sectional imaging studies to better estimate tumor size and local spread of disease to determine if a patient is an ideal candidate for surgery, and fertility-sparing surgery has evolved. Second, the increased use of sentinel lymph node biopsy allows for evaluation of lymph nodes in atypical locations that would have been missed with routine lymphadenectomy. In addition, the detection of micrometastasis, and the use of ultrastaging has led to a more accurate staging and determination for the need of adjuvant therapy. Third, improvements in adjuvant treatment options may have also lead to improving outcomes over time favoring the minimally invasive approach. Fourth, progress in treatment for patients with recurrent disease may have led to improving oncologic outcomes over time, and finally, better supportive and end-of-life care may have also influenced the reported outcomes in these series. As shown in the case series and reviews published, the follow-up time for open and minimally invasive approaches are often not balanced, with shorter follow up times in the minimally invasive groups, thus leading to fewer recurrences reported in such groups.

Moreover, none of the case series that compared oncologic outcomes between MIS and open radical trachelectomy adjusted for confounders using a statistical method. Patients in the MIS group tend to have smaller tumors, earlier disease stage, lower rates of lymph node involvement, and less need for adjuvant therapy than patients undergoing open surgery. Unadjusted or inadequately adjusted survival analyses are prone to be biased in favor of MIS as these factors are associated with a better prognosis.

It is not infrequent that centers have evaluated 'their own data', and propose no difference in recurrences when comparing both approaches. Radical trachelectomy is not a frequently performed surgery in gynecologic oncology. No multicenter, nor National Cancer Database study will be able to include enough cases to find a significant difference in oncologic outcomes between approaches, particularly noting that the recurrence rates, regardless of approach, is extremely small. One might consider that the reason for the equivalency between approaches may be due to some, or all of the variables mentioned in the previous paragraph (sample size, nonconcurrent surgeries, dissimilar follow-up time, patient selection bias) are unbalanced with a more favorable oncologic profile in the minimally invasive group and thus leading to the concern as to why outcomes are the same when the minimally invasive group is often a much more favorable group, thus suggesting that perhaps if larger numbers of patients were included, results might be similar to those of the LACC trial. A National Cancer Database study published in 2020 by Matsuo et al. [28], showed that fertility-sparing trachelectomy for young women with cervical cancer is a rare surgical procedure performed by only 89 centers in the United States from 2001 to 2011 and most hospitals (82%) perform <2 cases per year. Six hospitals (6.7%) accounted for the top decile centers performing >2.5 cases annually. The numbers published by the study by Matsuo et al. are per site, not per surgeon, which might be even smaller. As stated by Melamed et al. [29] in a recent publication titled *Minimally Invasive Radical Hysterectomy for Cervical Cancer: When Adoption of a Novel Treatment Precedes Prospective, Randomized Evidence*, "the

experience of a single surgeon or institution cannot produce estimates that are sufficiently accurate or precise to guide clinical practice".

In the aforementioned multi-institutional IRTA study, there are several items that should be highlighted. First, it is a retrospective prone to several biases related to this type of report. Patients were not randomized to receive open or MIS, but the decision was based on the surgeon's choice. Moreover, the fact that both groups were unbalanced, with the open group having more high-risk factors for recurrence and higher rates of adjuvant therapy, could have impacted the preliminary results thus far reported. Second, the sample size is also a point to consider. Although it is not accurate to perform a sample size calculation for a retrospective study as the length of follow-up time and accrual rate play an important role in determining sample size, in order to observe a statistically significant difference in 5-year survival rates, one would need to observe a total of 179 events. Given survival rates exceeding 90%, a total of 1382 patients would be needed in order to observe 179 events. Third, although surgeries included were performed in recent years, patients underwent surgery over a period of approximately 12 years at a rate of 4.4 patients/month. This shows the difficulty in performing a randomized prospective trial.

After the LACC Trial publication, at MD Anderson Cancer Center all patients scheduled for radical trachelectomies are recommended a laparotomic approach within an enhanced recovery after surgery (ERAS) protocol [30,31].

Ongoing conservative surgery trials in cervical cancer

The rationale for less radical surgery for early-stage cervical cancer is that several studies have shown that <1% of patients with early cervical cancer with favorable pathologic characteristics have parametrial involvement [32]. Less radical surgeries might offer an alternative to radical trachelectomy for some patients with early-stage disease. In addition, it has been shown that in approximately 60% of patients undergoing radical trachelectomy, the final pathologic specimen has no residual disease [33].

A review by Ramirez et al. [34] published in 2014, evaluated conization, simple hysterectomy, or simple trachelectomy as an alternative to radical surgery. The retrospective review included 260 patients with early-stage cervical cancer managed conservatively. The most common histology was squamous cell carcinoma 197 (75.8%) followed by adenocarcinoma 59 (22.7%) and most patients (80.4%) had FIGO 2009 stage IB1 disease. All patients underwent sentinel lymph node biopsy or pelvic lymphadenectomy. Follow-up time ranged from 1 to 168 months. At the time the report was published, two patients had relapsed, and one patient had died of recurrent disease.

Currently, three prospective studies are evaluating conservative approach in patients with low-risk early-stage cervical cancer. The ConCerv study (NCT01048853) is a prospective, multi-institutional international, not randomized (single arm) trial evaluating the safety and feasibility of conservative surgery in 100 patients with early-stage (IA2 or IB1) cervical cancer with tumor $\leq$2 cm, squamous cell carcinoma (any grade) or adenocarcinoma (grades 1 or 2). Patients with high-risk histology or LVSI were excluded. Treatment options were cervical conization and pelvic lymph node dissection (with or without sentinel lymph node (SLN) biopsy) for those desiring future fertility or a simple hysterectomy and pelvic lymph node dissection (with or without SLN biopsy) for those not interested in fertility. The primary objective was to evaluate the safety and feasibility of performing conservative surgery in this group of patients. Secondary objectives include assessing the treatment-associated morbidity and quality of life in patients undergoing conservative surgery compared with historical outcomes in matched patients treated with radical hysterectomy. The study completed accrual and preliminary results were presented in the IGCS 2019 meeting [35]. Positive nodes were found in 5/100 patients (5%) and 1/40 patients (2.5%) had residual disease in hysterectomy specimen following cone with negative margins. With 64% of patients having $\geq$2 years, the follow-up the recurrence rate was 4.3% (4/94).

The second ongoing study is a Gynecologic Cancer Intergroup (GCIG) study, the SHAPE Trial (NCT01658930). This is a randomized trial comparing radical hysterectomy and pelvic node dissection to simple hysterectomy and pelvic node dissection in patients with low-risk early-stage cervical cancer. The study included FIGO 2009 stage IA2 or IB1, tumors <2 cm, squamous cell carcinoma or adenocarcinoma, and less than 10 mm stromal invasion on Loop Electrosurgical Excision Procedure (LEEP)/cone biopsy or less than 50% stromal invasion on pelvic magnetic resonance imaging. All tumor grades

were allowed, and patients with LVSI were also eligible. Patients were randomized 1:1 to the control treatment (radical hysterectomy) or the experimental arm (simple hysterectomy). The primary objectives were to determine whether simple hysterectomy in patients with low-risk cervical cancer is safe and associated with less morbidity than radical hysterectomy and to determine whether overall survival is significantly different between the two arms of the study. The secondary endpoints included treatment-related toxic effects, extra pelvic relapse-free survival, overall survival, rate of sentinel node detection, rate of metastasis to the parametria, surgical margin status, pelvic node status, and quality of life. The study has completed accrual and results are anticipated in 2023.

The third ongoing trial is Gynecologic Oncology Group (GOG/NRG) protocol 278. This is a multi-institutional trial with the primary objective to determine the impact of nonradical surgery on the bladder, bowel, and sexual function and to determine the incidence and severity of lymphedema after nonradical surgery. Inclusion criteria include squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma, FIGO 2009 stage IA1 (LVSI positive), IA2, or IB1 disease; tumors $\leq$2 cm, and any grade. All patients must have had a cone biopsy or loop electrosurgical excision procedure with margins negative for carcinoma and high-grade dysplasia. In this study, patients are stratified according to their wish for fertility preservation to either cone biopsy and pelvic lymphadenectomy or simple hysterectomy and pelvic lymphadenectomy. This study is still ongoing and continues to accrue patients.

Summary

Radical trachelectomy is a feasible alternative to radical hysterectomy for patients with early-stage cervical cancer wishing to preserve fertility. Retrospective studies have shown that it has similar oncologic outcomes as the standard radical hysterectomy. Published data supports that radical trachelectomy may be performed via the vaginal, open abdominal, or minimally invasive approach. A prospective randomized trial evaluating open vs. minimally invasive approach is unlikely given the rarity of the procedure and the large number of patients required for such trial. Preliminary results from the largest retrospective international collaboration study (IRTA), have shown similar progression-free and overall survival for patients with tumors up to 2 cm undergoing open vs. minimally invasive radical trachelectomy. Results from three ongoing prospective trials of patients with early-stage cervical cancer undergoing less radical surgery (conization or simple hysterectomy) are to be reported soon. These three important trials will provide evidence as to the role and oncologic safety of conservative management in patients with early cervical cancer categorized as low risk. Such results may change the standard of care toward either conization or simple hysterectomy instead of radical trachelectomy or hysterectomy for qualified patients.

Practice points

- Radical trachelectomy is a safe and viable option for fertility preservation in patients with early cervical cancer and tumors <2 cm
- Ideal candidates for radical trachelectomy are patients with squamous or adenocarcinoma histology, no lymph node or distant metastases and interested in future fertility
- The predominant approach to radical trachelectomy is a minimally invasive approach either through laparoscopy or robotic surgery
- Retrospective data indicates that there are similar oncologic outcomes between open and minimally invasive radical trachelectomy.
- Options for more conservative approaches including conization and sentinel lymph node mapping are being explored in prospective trials

Research agenda

At this time we know from the published literature that based on retrospective data, radical trachelectomy is safe and feasible via a vaginal, open, or minimally invasive (laparoscopy or robotics) approach and that the trend seems to have favored a minimally invasive approach. Data for oncologic outcomes seem similar among these groups, as evidenced by similar recurrence rates, disease-free survival, and overall survival. We also know that ideal candidates are patients wishing to preserve future fertility, with squamous or adenocarcinoma, tumor size <2 cm, with no evidence of distant metastatic disease.

There are gaps in knowledge, and further research is needed to answer important questions. These include whether there is a group of patients that may be a higher risk of recurrence when undergoing radical trachelectomy. We also lack accurate selection criteria data that allow us to predict which patients will require adjuvant treatment post radical trachelectomy. Lastly, we await results of prospective trials to determine whether even more conservative approaches such as conization or simple hysterectomy are feasible options in low-risk patients with early-stage cervical cancer.

Conflicts of interest

The authors have no conflicts of interest or financial disclosures to declare.

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