Gynecologic Oncology 165 (2022) 169–183

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Oncologic results of fertility sparing surgery of cervical cancer: An updated systematic review

P. Morice [a,b,c,*], A. Maulard [a], S. Scherier [a], C. Sanson [a], J. Zarokian [a], F. Zaccarini [a], S. Espenel [d], P. Pautier [e], A. Leary [e,f], C. Genestie [g], C. Chargari [b,d], M. Grynberg [c,h], S. Gouy [a]

[a] Department of Gynecological Surgery, Gustave-Roussy, Villejuif, France
[b] Inserm Unit 10-30, Gustave-Roussy, Villejuif, France
[c] University Paris-Sud (Paris XI), Le Kremlin-Bicêtre, France
[d] Department of Radiation Oncology, Gustave-Roussy, Villejuif, France
[e] Department of Medical Oncology, Gustave-Roussy, Villejuif, France
[f] Inserm Unit 981, Gustave-Roussy, Villejuif, France
[g] Department of Pathology, Gustave-Roussy, Villejuif, France
[h] Department of Reproductive Medicine, Hôpital Antoine-Béclère, Clamart, France

HIGHLIGHTS

- In stage IB1 cervical cancer, the recurrence rate observed after simple cone/trachelectomy is 4%.
- In stage IB2 disease, the lower rate of recurrence is observed after radical trachelectomy by abdominal approach.
- In stage IB2 disease, the highest recurrence rate is observed after neo-adjuvant chemotherapy and conservative surgery.
- The lower fertility results are observed after radical trachelectomy by laparotomic approach.

ARTICLE INFO

Article history:
Received 7 December 2021
Received in revised form 12 January 2022
Accepted 17 January 2022
Available online 28 February 2022

Keywords:
Early-stage cervical cancer
Conservative treatment
Conisation
Trachelectomy
Neoadjuvant chemotherapy
Fertility
Prognostic factor
Radical trachelectomy
Recurrence

ABSTRACT

Background. Several techniques can be proposed as fertility sparing surgery in young patients treated for cervical cancer but uncertaincies remain concerning their outcomes. Analysis of oncological issues is then the first aim of this review in order to evaluate the best strategy.

Results. Data were identified from searches of MEDLINE, Current Contents, PubMed and from references in relevant articles from January 1987 to 15th of September 2021. We carry out an updated systematic review involving 5862 patients initially selected for fertility-sparing surgery in 275 series.

Findings. In patients having a stage IB1 disease, recurrence rate/RR in patients undergoing simple conisation/trachelectomy, radical trachelectomy/RT by laparoscopico-vaginal approach, laparotomic or laparoscopic approaches are respectively: 4.1%, 4.7%, 2.4% and 5.2%. In patients having a stage IB2 disease, RR after neoadjuvant chemotherapy or RT by laparotomy are respectively 13.2% and 4.8% ($p = .0035$). After neoadjuvant treatment a simple cone/trachelectomy was carried out in 91 (30%) patients and a radical one in 210 (70%) cases. But the lowest pregnancy rate is observed in patients undergoing RT by laparotomy (36%).

Conclusions. The choice between these treatments should be based above all, on objective oncological data that strike a balance for each procedure between the best chances for cure and the fertility results. In patients having a stage IB1 disease, oncological results are quite similar according to the procedure used. In patients having a stage IB2 disease, RT by open approach has the lowest RR. Anyway the lowest pregnancy rate is observed in patients undergoing RT by laparotomy.

* Corresponding author at: Department of Gynecological Surgery, Gustave-Roussy Cancer Campus, 114 rue Édouard-Vaillant, 94805 Villejuif Cedex, France.
E-mail address: philippe.morice@gustaveroussy.fr (P. Morice).

https://doi.org/10.1016/j.ygyno.2022.01.023
0090-8258/

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1. Introduction

Prognostic factors of early stage cervical cancer are clearly identified: tumor size (related to the 2018 FIGO staging system with a cutoff at 20 and 40 mm), the nodal status, the lympho-vascular space involvement status (LVSI), the depth of stromal invasion and, more recently, as showed in a large randomized trial with unexpected results, the surgical approach [1–3]. The standard surgery comprises then a hysterectomy combined with nodal staging surgery that could be a full pelvic lymphadenectomy or a selected nodal dissection with sentinel lymph node (SN) biopsy, currently evaluated in several trials over the globe [2].

Nevertheless, following the initial description of Novack and Aburel, improved thereafter by Daniel Dargent in the mid 80s as radical trachelectomy (RT), fertility-sparing surgery (FSS) (to keep in place the uterine corpus and adnexae removing the cervical disease to allow subsequent pregnancy) lead to an impressive increasing global concern in young patients affected by early stage cervical cancer [4,5]. Such FSS involves in fact different 6 technical procedures: the initial one was reported by Daniel Dargent combining a laparoscopic step to carry out the lymph node dissection and thereafter the RT by a vaginal approach (VRT) RT by laparotomic approach, widely used by many teams, RT by pure laparoscopic and, more recently, robot-assisted laparoscopic approach. All these procedures include a parametrial dissection, explaining then the wording "radical", to qualify the trachelectomy. The last two procedures are simple: cone/trachelectomy (without any parametrial dissection), and an initial neoadjuvant chemotherapy (NACT), followed by a cervical resection (that could be a simple or radical conisation/trachelectomy). Whatever the strategy preferred, all these procedures should be used in patients with early-stage disease without any extracervical disease (particularly a nodal and/or parametrial one) and with "good" prognostic factors (combining the histologic subtypes, the tumor size, depth of stromal invasion and LVSI status) to allow these patients to be safely treated by exclusive FSS without adjuvant treatment [5].

Six years ago, we published a full review of the literature dedicated to oncologic issue and fertility issues after FSS [5,6]. The key messages of these papers, with the knowledge of the literature from the mid 2010s, were firstly to report a very low recurrence rate in patients treated with simple cone/trachelectomy (a single ambiguous recurrent disease reported at that time), valiting then this concept. Furthermore, VRT procedure is "safer" in patients with tumor size <20 mm, but with no statistical difference in terms of recurrence, in patients with LVSI. At last, in case of patients with tumor size between 20 and 40 mm (current stage IB2 according to the 2018 FIGO classification[3]), the preferred strategy should be NACT instead of RT by laparotomic approach (similar rate of recurrences, but higher fertility results in the first option) [5,6].

Since that date, many reviews and/or meta-analysis have been published (just for the last months [7–13]). Criteria to select papers in these reviews were different from one to the other, adding sometimes in one calculation cases and data from the same institution, but published at different periods. Impacts of these papers to choose between the 6 previous strategies in 2021 remain unclea. As many papers and new series had been published during the past few months, we decided to update our previous review with the same methodology that we used initially, which required to perform a systematic review and analysis of all published series and case reports in order to try to use the results obtained to measure accurately the recurrences rates, fertility results and then define the potential indication for each procedure used for FSS. The first aim of this update review is then to clarify the oncologic outcomes for each procedure and therafter to discuss their fertility results.

2. Data collection

2.1. Search strategy and selection criteria

Data were identified from searches of MEDLINE, Current Contents, PubMed and from references in relevant articles from 1987 to September 15, 2021, using the following search terms: "early-stage cervical cancer", "conservative surgery", "conservative treatment", "fertility-sparing surgery", "trachelectomy", "radical trachelectomy", "laparoscopic trachelectomy", "laparot* trachelectomy", "robot* trachelectomy", "abdominal trachelectomy", "neoadjuvant chemotherapy", "conisation" and "cone resection". Only articles published in English, or having a detailed abstract in English, were included. The series comprising the largest number of patients (or the most complete data) was retained for repeated publications by the same team, We excluded the specific management of paediatric tumors. Papers exclusively focused on a technical description without any follow-up >12 months (if no intercurrent event reported in the paper-meaning pregnancy or recurrence) were not included (excepting in the case of a new procedure described for the first time). Pure reviews of the literature and analyses of national cancer registry or epidemiologic database having unsufficient data to study precise specific characteristics of recurring patients, were not included in the current analysis. The design of this systematic review of the literature is done in accordance with the PRISMA

guidelines. The PRISMA flow diagram detailing the selection and exclusion criteria of papers is presented in Supplementary Fig. 1.

2.2. Analysis

The first and the last authors extracted and analysed the different series. The main issue of this review is to focus on the oncologic outcomes. The analysis comprises the patients' characteristics (tumor size, stage, histological subtype, LVSI status, depth of stromal invasion, and margins status if known), specific surgical aspects (approach, preservation or not of the uterine artery, cerclage…), major morbidities (related to the lymphadenectomy and the cervical procedure) and characteristics of recurrent disease. Concerning the FIGO staging system, we integrate the FIGO classifications used in publications. However, regarding the most simple procedure (simple conisation/trachelectomy) -as the key issue is to evaluate the results of FSS for invasive carcinoma- we excluded papers involving only stage-IA disease. We then try also to convert into 2018 FIGO staging[3] whenever possible (Table 1). The overall survival could not be studied, since we had very few data about the long-term outcomes of recurring patients after such strategies, explaining then the wide discrepancy between number of recurrences and number of deaths.

Recurrences reported in different tables of this paper are observed in patients undergoing successfully their FSS without adjuvant treatment depriving them definitively of their fertility potential (external radiation therapy +/− concurrent chemotherapy and/or hysterectomy). Recurrence rates are calculated involving series reporting their cases and the number of recurrences (if observed). We also calculate this rate according to the tumor size (< or ≥20 mm to follow the cutoff of the 2018 FIGO staging system) integrating series reporting details about the tumor sizes distribution and exact initial characteristics of recurrent patients, if observed (particularly initial tumor size). Whenever possible, we calculate this rate for LVSI status, but this evaluation was not possible for the depth of stromal invasion, because of a lack of sufficient data.

Major metrics of fertility results are also included, since they should be put in mirror of the oncological issues to have a complete overview. Pregnancy rate (PR) was determined in series with complete data on the total number of patients attempting to become pregnant and the number of them succeeding. Live birth rates (LBR) are determined in series with complete data about the total number of pregnancies (excepting ongoing pregnancies without outcomes reported) and the number of live births. Prematurity rates (PTR) are determined in series with complete data about the number of live birth deliveries and the number of premature deliveries. But due to a lack of place, prognostic factors for fertility results (that are not directly linked to the first aim), have not been then included in the current analysis.

As a limited space for tables and figures is allowed, longest tables reporting the most described procedures (VRT, Open RT) were added in the supplementary materials. Similarly, table reporting the most recent procedure (robot-assisted RT) was added in the supplementary materials. References of these tables are then included at the final part of the supplementary materials. As a limited number of references are allowed for this review, all references in case reports (reporting ≤3 cases) or the initial series of teams who updated their reports several times in the tables, are included in the supplementary materials.

3. Findings

3.1. Vaginal RT

We begin by this procedure that is historically the first one reported. Table 1 of the supplementary materials details the series devoted to VRT [4]. About 2150 cases were reported by more than 35 teams. At least 250 patients have been excluded (few series had not mentioned this figure), on the basis of intermediate or poorer prognostic factors, because they had finally received an adjuvant treatment or had undergone a completion hysterectomy (mainly for positive margins)(Supplementary Table 1) [4].

A majority of patients had stage-IB (FIGO 2018) disease, but few stage-IIA1 were included. A majority of stage-IB1 tumors measured <20 mm, but at least 101 cases had stage-IB2 lesions >20 mm; were observed (reporting their outcomes). Peroperative morbidities were scarcely reported: several cases of bleeding or vessel injuries or urinary tract injuries (>30 cases). The main postoperative morbidities were related to the lymphadenectomy and were observed with all types of FSS (lymphocysts and lymphoedema) or related to the cerclage used by a majority of teams after removing the cervix (cervical stenosis and cerclage erosion).

Among patients who finally underwent FSS (by definition node-negative cases), 86 recurrences and 27 deaths were observed. Three recurrences were reported in patients with a small neuroendocrine tumor. The recurrence rate is 5.1%. Two main factors for recurrence were analysed: the tumor size (< or >20 mm) and LVSI status. In series reporting clearly the tumor size and characteristics of their recurrent disease (if observed), among 1037 patients having stage IB1 disease 48 (4.7%) recurrences were observed, *versus* disease 21/101 (20.7%) for stage IB2 ($p < .00001$). Concerning the impact of LVSI status (independently from disease stage), the recurrences rates were respectively in patients with or without LVSI 14/592 (2.4%) and 19/266 (7.1%) ($p < .001$). But we do not have data about the impact, according to the number of LVSI foci, their location (inside the tumor or around it) and their type (vascular or lymphatic). PR, LBR and PRT were respectively 58.7%, 71% and 30%.

3.2. Patients with a stage-IB1 tumor ≤20 mm: a simple trachelectomy or conisation

Table 1 shows all the cases of such management in stage-IB1 disease: 649 patients were published by 23 different teams (Table 1) [14–33]. As we mentioned previously, all papers reporting exclusively the management of stage-IA disease were excluded, but in scarse series reported in the current table focusing on stage-IB disease, few stages-IA disease were mixed to stage IB1, and discrimination of specific results for invasive carcinoma is difficult. Logically, all of them reported a tumor size ≤20 mm. All patients underwent a pelvic lymph node dissection (total pelvic lymphadenectomy or sentinel node dissection). Nearly 60 patients were excluded because of nodal involvement. Nearly 200 cases had LVSI. All cervical resections were done using a vaginal approach, except one team using an abdominal approach.

Eighteen (4.1%) recurrences were observed (in patients treated successfully for this conservative management) and 1 death was reported. The location of the recurrent disease was: cervix in 12 patients, nodal in 4, ovarian in 1, and parametria in 1. It is impossible to evaluate accurately the risk of recurrence according to LVSI status (because very few series reporting the LVSI status in stage lesion and specified as initial prognostic factor in recurring cases). But interestingly, among recurrent patients, 6 had initially LVSI, 6 had not, and this status is unknown in 6 others. PR, LBR and PRT were respectively 56.3%, 88% and 18.2%.

3.3. Neoadjuvant chemotherapy (NACT) followed by conservative surgery

Table 2 summarizes all the cases reported on NACT [21,22,34–49]. Among the 337 cases reported that were selected for this management, 301 underwent eventually uterine conservation. Simple cone/trachelectomy (by vaginal approach except in one team using abdominal approach) was carried out in 91 (30%) patients and a radical one in 210 (70%) cases (vaginal, open or mini-invasive) (Table 2). A majority of patients had stage-IB1 or 2 diseases, but at least 51 and 11 had a stage-IB3 or IIA disease. Among patients with stage-IB1 and 2 diseases, 113 had a tumor size <20 mm, and 147 between 20 and 40 mm. A majority of patients received 3 courses of platinum-based chemotherapy. Three teams administered direct intra-arterial (intrafemoral or intra-uterine artery) chemotherapy combined in one with intravenous chemotherapy. Chemotherapy

Table 1
Literature review of a cone resection or simple trachelectomy as conservative management for stage IB1 cervical cancer.

Authors-Years	N cases	Tumor size mm or 2018 FIGO stage	Histological subtype	Depth stromal invasion Median in mm	LVSI status	Lymphadenectomy	Cervical surgery	Fertility results	Outcomes [****,*****] (Median)
Dhar 2003	1	10 × 1	SCC	1	Positive	PLND	Conisation	2 pregnancies 1 T1 loss	NED 41 months
Maneo 2011 [14]	37/36	All IB1 Median 11.7	24 SCC, 12 ADC	4 (range 1.5–13)	5 Positive	PLND (1 N+)	CKC/LEEP/Laser conisation	21 pregn. in 17 pts. 14 live birth & 1 ong. 4 T1 loss 1 T2 loss 1 interruption 3 preterm delivery	2 recurrences (1 nodal and 1 local) 1 having LVSI FU 66 months
Raju 2012 [15]	10	All IB1 Mean 8 [***]	9 SCC, 6 ADC[***]	No specific data	0	PLND	Simple trachelectomy	5 pts. attempting 4 live birth pregn.[*****]	No recurrence. FU 96 months[******]
Naik 2007, Biliatis 2012[*] [16]	35	Small volume Median 9.75[*****]	49 SCC, 11 ADC, 2 ADS[******]	1.55 (range 0.3–5)[******]	14 Positive[******]	PLND in 31	LLETZ	7 live birth pregn.	No recurrence. FU 56 months[******]
Al-Kalbani 2012 [17]	6	All IB1	6 ADC		4 positive[***]	6	LLETZ or cone	No data	No recurrence FU 36 months[******]
Palaia 2012 [18]	9	All IB1	11 SCC, 3 ADC[***]	17 (range 14–19)	0	PLND	Extrafascial trachelectomy	8 pregn.in 8 pts. 5 preterm delivery 3 term delivery	No recurrence FU 38 months[******] 1 death other cause
Lindsay 2014 [19]	37	All IB1	28 SCC, 11 ADC, 4 ADS[***]	No specific data	16 Positive[***]	PLND (1 N+)[***]	LLETZ [***]	19 pregn. in 16 pts. 1 T1 loss 1 interruption 15 live birth and 4 ong. 4 preterm delivery	1 local recurrence (having LVSI) FU 42 months[******]
Andikyan 2014	3	8.8 & 11	SCC	2, 4 & 8	0	SLN alone	Conisation	3 pregnancies	No recurrence. FU 17 months[******]
Bouchard-Fortier 2014 [20]	29[***]	Exact number of IB1 treated conservatively? Median 10[*******]	26 SCC; 22 ADC; 3 ASC[*******]	2 (range 0.6–12)[*******]	18[*******]	PLND or SLND (1 N +)	Cone biopsy	No data	No recurrence FU 21 months[*******]
Choi 2014 [21]	5	IB1	3 SCC, 1 AD, 1 ADS	No specific data	3	PLND, PALND in 1	Conisation & photodynamic therapy	3 pts. attempting 3 pregnancy in 3 pts. 1 early preterm deliv (25 WG) 1 preterm (28 WG) 1 full term deliv	1 recurrence (nodal) FU 55 mths
Slama 2016 [22]	44/32[***]	22 IB1	26 SCC, 4 ADC; 2 ASC[********]	No specific data	6[********]	SLND + PLND (7 N +)[********]	Simple trachelectomy/Cone biopsy	9 pts. attempting. 6 pts. pregn. 1 T1 loss. 1 preterm labor & 4 full term deliveries	1 recurrence (ovary) AWPD FU 23 months[********]
Okugawa 2017 [23]	14/11[*********]	1 IB1	4 SCC, 9 ADC, 1 ADS[*********]	No specific data	No specific data	SLND[***]	Abdominal simple trachelectomy	1 pregnancy in stage IB1 disease	No recurrence FU 61 months[***]
Tomao 2018 [24]	59/53[***]	41 IB1	33 SCC, 19 ADC, 2 ASC[***]	No specific data	12 positive[***]	PLND[***]	CKC/Laser conisation	25 pts. attempting 20 pregn. in 17 pts. 19 live-born babies	5 recurrences (4 cervix and 1 node) 2 had LVSI FU 55 months[***]
Demirkiran 2018 [25]	14/13[***]	7 IB1	12 SCC; 2 ADC[***]	No specific data	7 Positive[***]	SLND +/− PLND	Simple trachelectomy	11 pts. attempting 7 achieving pregnancy 4 Term birth; 2 premature delivery, 1 T1 loss	No recurrence FU 27 months[***]
Plante 2013,2017,2020 [26]	50[***]	26 IB1	10 SCC; 16 ADC 1 ASC; 3 others[***]	No specific data	15 Positive[***]	SLN in 15 + PLND in 35[***]	Simple trachelectomy/large CKC	40 pregn. in 27 pts. 30 full-term; 3 preterm 6 foetal loss and 1 on-going	1 nodal recurrence (ITC on SLND) FU 76 months
Li 2020 [27]	40[***]	14 IB1	35 SCC; 3 ADC; 2	4 (range, 1–4)	15	PLND	LEEP/Conisation	17 pts. attempting.	No recurrence

			ASC***	=	Positive***		/reconisation	4 pts. pregn.	FU 35 months***
Lee 2020	2	IB1	No specific report	–	–	–	–	–	No recurrence
Ditto 2015, Bogani 2019, Martinelli 2021 [28]	39/33***	25 IB1	22 SCC; 17 ADC***	4 (range, 1–8)***	15 Positive***	SLND or PLND	Laser conisation/ Reconisation	22 pts. attempting 12 achieving 13 pregnancies 10 live birth (9 at term) 1 T1 loss; 1 T2 loss 1 interruption	2 recurrences (cervix) 1 having LVSI FU 51 months
Nica 2021 [29]	44/38***	20 IB1	27 SCC; 16 ADC; 1 ASC***	2.3 (range 0.3–8)***	18 Positive***	SLND	Conisation	30 pts. attempting 20 pregnancies in 13 pts. 17 live births (16 at term)	No recurrence FU 44 months
Ferrandina 2008, Fagotti 2011, Fanfani 2021 [30]	52/35	All IB1 Median size 11 mm	27 SCC; 13 ADC; 2 ADS	No specific data	15 Positive	SLND or PLND	LEEP/CKC	22 pts. attempting 14 pregnancies in 12 pts. 12 live births (6 at term) 1 T1 loss; 1 T2 loss	3 recurrences (2 cervix and 1 parametrial) 1 having LVSI FU 54 months
Pluta 2009, Rob 2008, Rob 2011, Hruda 2021*[31]	68/61**,***	68 IB1**********	66 SCC, 20 ADC, 4 ADS***	< 50% (MRI)	26 Positive	SLN followed by PLND (9 N+)***	Simple trachelectomy	23 pregn. in 17 pts. 12 deliv. and 3 on-going*** 5 T1 loss 3 T2 loss	1 isthmic recurrence DOD FU 149 months***
Breban 2021 [32]	5	All IB1	No specific data	NR	1	SLND or PLND	Simple trachelectomy	3 attempting 3 pregnancies in 2 pts	No recurrence
Schmeler 2021 [33]	46***	31 IB1	No specific data	No specific data	No	SLND or PLND	Cone biopsy	14 pregnancies in 11 pts. 13 full term; 1 T2 loss	1 recurrence (cervix) FU 36 months******

SCC: Squamous Cell Carcinoma; ADC: Adenocarcinoma; ASC: Adenosquamous Carcinoma; SLN: Sentinel Lymph Node; PLND: Pelvic Lymph Node Dissection: LVSI: Lympho-Vascular Space Involvement.
LEEP: Loop Electrical Excision Procedure; LLETZ: Large Loop Excision of the Transformation Zone; CKC: Cold Knife Conisation; N+ Nodal involvement.
NED: No evidence of disease; FU: Follow-up; T1: 1st Trimester of the pregnancy; T2: 2nd Trimester of the pregnancy
Recurrences reported are observed in patients treated without adjuvant treatment depriving her fertility potential.

* In case of repeated publications by the same team/group of authors, the last updated data (or the data reported in the largest series) are given in the table.
** The initial figure concerns patients scheduled for fertility sparing management (FSM) and the second one, patients who finally underwent FSM (for IB1 disease).
*** Including stage IA & IB1.
**** All FU times are medians except for the series by Ditto et al.
***** Recurrences reported are observed in pts. treated conservatively for stage IB1 disease.
****** Data given for the entire population.
******* Including patients treated conservatively and radically.
******** Including 9 cases treated with neoadjuvant chemotherapy.
********* Patients having Abdominal simple Trachelectomy.
********** Stage IB1 according to 2009 classifiaction.

Table 2
Literature review of neoadjuvant chemotherapy followed by conservative management for stage I/II cervical cancer.

Authors-Years	Number cases	FIGO Stage (2018) tumor size mm	Histological subtypes	Chemotherapy type	Number courses	Surgery after NACT	Histology cervix	Fertility results	Outcomes mths
Kobayaski 2005	1	IB2 30 mm	SCC	Cisplatin, Bleomycin, Vincristine, Mitomycin	4	CKC	No RD	Spontaneous pregnancy	NED 48 mths
Plante 2006, 2011 [34]	4	IB2 (30,30 & 40 mm) and 1 > 30 mm	SCC in 3	3 Cisplatin, Pacxlitaxel, Ifosfamide 1 Cisplatin, Gemcitabine	3	PLND + VRT	No invasive RD in 3	4 pregnancies in 3 pts. 1 T1 loss	NED
Liu 2008	1	IB1 20 mm	SCC	Cisplatin, Bleomycin	1	PLND + ART	Focal carcinoma 5 mm	Pregnancy	Not reported
Singh 2011	1	IB2 35 mm	Clear cell ADC	Carboplatin, Paclitaxel	3	PLND + VRT	RD 20 mm	Currently14-years-old	NED 14 mths
Palaia 2011	1	IB3 55 mm	SCC	Cisplatin, Paclitaxel, Ifosfamide	3	PLND + SVT	No invasive RD	Not planned	NED 18 mths
Tsubamoto 2012	3	1 IB2 32 mm 2 IB3 43, 60 mm	3 SCC	1 IV Nedaplatin & intrauterine artery Cisplatin 2 IV Irinotecan and intrauterine artery Cisplatin	3	PLND + SVT	No RD	No data	NED 65, 86, 120 mths
Landoni 2007, 2012 [35]	21/16[**]	IB2 < 30 mm	9 SCC	9 Cisplatin, Pacxlitaxel, Ifosfamide			8 No invasive RD	9 pts. attempting	
Maneo 2008[*] [35]		(8 ≥ 20 mm)	12 ADC	12 Cisplatin, Pacxlitaxel, Epirubicin	3	PLND + CKC	9 RD < 3 mm 4 RD > 3 mm	10 pregn. in 6 pts. 1 T1 loss 2 preterm delivery	1 recurrence (nodal)[***] Mean FU 69 mths
Hamed 2012	1	IB3 60 mm	SCC	Cisplatin, Paclitaxel	4	P & PA LND + Robotic RT	No invasive RD	–	NED 16 mths
Wang 2012	2	IB2 25 & 35 mm	SCC	1 Cisplatin, 5 FU 1 Bleomycin, Cisplatin	1	PLND + VRT	1 no invasive RD 1 RD 12 mm	Patients did not attempt to conceive	NED 69 & 96 mths
Tsuji 2013	1	IB3 > 40 mm	SCC	Intra-arterial (femoral) Cisplatin, Mitomycin	2	PLND + ART	Microinvasive RD	Pregnancy with IVF	NED 64 mths
Gottschalk 2011 [36]		14 IB2 (>2 cm)	11 SCC	1 Cisplatin, Paclitaxel		RVT (in 18 pts)[****]	9 No invasive RD	7 pts. attempting 7 pregnancies in 5 pts	
Vercellino 2012 [36]	20	5 IB3	8 ADC	19 Cisplatin, Paclitaxel, Ifosfamide	2 or 3	2 not yet done	4 RD ≤ 5 mm	2 T1 loss	1 recurrence (local)
Lanowska 2014[*] [36]		1 IIA1	1 ASC				4 RD > 5 mm	2 Premature deliveries	Mean FU 23 months
Van Gent 2014	3	3 IB3	3 SCC	Cisplatin, Paclitaxel	6 (weekly)	PLND, ART (nerve sparing)	RD 3, 4 & 5 mm	3 deliveries in 2 pts	NED 6, 23 & 63 mths
Choi 2014 [21]	5	4 IB 2, 1 IIA1	5 SCC	Cisplatin + Etoposide or Paclitaxel	3	PLND + Conisation + Photodynamic therapy	1 had RD > 2 cm	4 pts. attempting 2 pregnancies in 2 pts. At term delivery	No recurrence FU 60 mths
Salihi 2015 [37]	11/9[**]	7 IB1 3 IB2	6 SCC	2 Cisplatin, Paclitaxel, Ifosfamide	3[*****]	7 CKC[****]	8 No RD	9 pts. attempting 11 pregnancies in 6 pts	
		1 IB3	4 ADC 1ASC	9 Carboplatin, Paclitaxel		3 Laser conisation	2 RD (1 with involved margins) 1 Progressive disease not undergoing conisation	4 T1 loss and 2 premature deliveries	1 recurrence (local) FU 58 mths
Saadi 2015	1	IB2 31 mm	SCC	Cisplatin, 5 FU, Ifosfamide	3	Laparoscopic RT[****]	RD 20 mm	No data	NED 9 mths[******]
Hauerberg 2015	1	IB3 45 mm	ADC	Cisplatin, Ifosfamide, 5 FU	Unknown	PLND + VRT	Unknown	Unknown	NED 68 mths
Estevez 2015 [38]	5/4	5 IB2	5 SCC	3 Cisplatin, Paclitaxel, Ifosfamide 1 Cisplatin, Pacliatxel	3	PLND +4 conisation & 1 VRT	2 No RD 2 RD < 5 mm	0	NED FU 19.5 mths
Feng 2016	1	IB3	SCC	Cisplatin, Paclitaxel	3	P & PA LND + conisation	No RD	1 pregnancy with PROM Delivery at 29 WG	NED FU 72 months
Slama 2016 [22]	10/9	7 IB2/ 2 IB3	Mixed with simple trachelectomy	Cisplatin, Ifosfamide (SCC) Cisplatin, Doxorubicin or Paclitaxel (ADC) Dose dense	NR	Initial PLND + SN Conisation or reconisation		Results mixed with simple trachelectomy	3 recurrences (local) 1 DOD FU 23 mths

Yan 2016 [39]	60	60 IB1	55 SCC 5 ADC	Cisplatin + Paclitaxel		PLND + VRT		42 pts. attempting 42 pregn. in 36 pts. 36 live birth 6 1st or 2nd trimester misc.	1 recurrence FU 43 mths
Poka 2017	1	1 IB2 30 mm	NEC	NR	NR	PLND + ART	NR	No	Recurrence at 3 mths DOD
Marchiole 2011, 2018 [40]	19	10 IB2 5 IB3	11 SCC	Cisplatin, Pacxlitaxel, Ifosfamide			7 no RD	5 pts. attempting 8 pregnancies in 3 patients	2 recurrences (local) IB2
		4 IIA1	8 ADC	Cisplatin, Pacxlitaxel, Epirubicin	3 or 4	PLND + VRT	5 < 3 mm 5 > 3 mm	3 live birth 4 T1 foetal loss 1 interruption	FU 79 mths
Robova 2010, 2014, 2019[*41]	40/29[**]	At least 20 stages IB1 & 2 At least 7 > 4 cm	At least 15 SCC At least 13 ADC	Cisplatin, Ifosfamide (SCC) Cisplatin,Doxorubicin or Paclitaxel ADC) Dose-dense	3	PLND + SVT	6 No RD 11 RD < 3 mm 11 RD > 3 mm	23 pregnancies in 19 pts. 19 babies	5 recurrences (4 local and 1 ovarian). 3 DOD FU 42 mths
Lu 2014, 2019 [42]	13	IB2 > 20 mm	12 SCC, 1 AD	Intra-arterial Cisplatin, Bleomycin, Mitomycin	2	PLND + Laparoscopic RT	Response >50% for all 2 adjuvant chemotherapy	4 pts. attempting., 2 pregnancies (1 T1 loss, 1 premature delivery)[****]	No recurrence NED 66 mths[****]
Wang 2019 [43]	17	IB2 or IIA1	No specific report	Cisplatin, Bleomycin, Vinblastine	1 or 2	PLND + Laparoscopic RT	NR	NR	No specific report
Tesfai 2020 [44]	19/15	9 between 2 and 4 cm 4 IB3 2 IIA 1 & 2	14 SCC 5 ADC 5% Clear Cell	Cisplatin, Paclitaxel weekly	3	15 PLND & ART Nerve sparing	5 no RD 4 RD < 3 mm 7 RD > 3 mm 3 stable disease	3 patients had 8 pregnancies 6 live birth & 2 interruptions	2 recurrences (1 local & 1 loco-regional) 2 DOD FU at 50 mths
Okugawa 2017, 2020 [45]	11/9	≥20 mm (IB) or IIA1	Mixed with others managements	Carboplatin, Paclitaxel	–	Abdominal approach	NR	2 patients had 4 pregnancies (3 ICSI and 1 IVF). One 1st trim. misc. 1 delivery at 33 WG & 2 at 37 WG	NED at 61 months
Rendon 2021 [46]	25/23	17 IB1 (FIGO 2009) 7 IB2 (FIGO 2009) 1 IIA1	23 SCC 2 ADC	Cisplatin, Paclitaxel (7 pts) Carboplatin, Paclitaxel (8 pts) Cisplatin, Pacliatxel, Ifosfamide (4 pts) Others combination (5 pts)	Median 3	PLND & 11 ART 9 LRT 5 conisation	11 no RD 14 RD	10 pregnant patients 4 term delivery 7 preterm births 1 interruption 1 ongoing 2 unknown	3 recurrences (1 local, 1 nodal, 1 nodal & ovarian) FU at 47 mths
De Vicenzo 2021 [47]	13/11	11 IB2 2 IIA1	7 SCC 6 ADC	Cisplatin, Paclitaxel	3	9 PLND and 4 SN 11 conisation/ 4 reconisation	3 no RD 6 microscopic D 2 macroscopic D	3 pts. attempting 2 pregnant patients 1 premature delivery (34 WG)	1 recurrence (distant) FU at 37 mths
Zusterzeel 2020, Aarts 2021 [48]	22/17	All IB2 1 during pregnancy	16 SCC 6 ADC	Cisplatin, Paclitaxel Weekly	6 courses	Robot PLND + VRT	7 no RD	8 pts. attempting 6 pregnancies 4 live birth 1 preterm 2 abortions	3 recurrences (1 local, 1 local-regional, 1 distant) FU 53 months
Sanson 2021 [49]	4/3	All IB2 ≤ 30 mm	4 SCC	Carboplatin, Paclitaxel	3 courses	Initial PLND VRT in 1 Conisation/ Trachelectomy in 3	1 no RD 3 had RD > 3 mm	1 pt. attempting No pregnancy	1 recurrence (local) FU 26 mths

IVF: *In Vitro* Fertilization; IUI: Intra-uterine Insemination. FU: Follow-up. DOD: Died of Disease; T1: 1st Trimester of the pregnancy.
Recurrences reported are observed in patients treated without adjuvant treatment depriving her fertility potential.

* In case of repeated publications by the same team/group of authors, the last updated data (or the data reported in the largest series) are given in the table.

** The initial figure concerns patients scheduled for fertility sparing surgery (FSS) and the second one, patients who finally underwent FSS.

*** For this patient, whether initial was neo-adjuvant or adjuvant chemotherapy combined with FSS is unclear.

**** Results analysed from the first series.

combined initially 3 drugs (in majority: platinum based, paclitaxel and ifosfamide) in the intial years, but during the last 5 to 10 years, 2 drugs only were used (carbo or cisplatinum and paclitaxel). Chemotherapy toxicities were moderate and managable (mainly haematological).

Concerning the surgical approach reported to remove the cervical disease, a majority of teams used a vaginal approach, a laparoscopic approach (4 teams), a robotic one (1 team) and even a laparotomic one (7 teams) (Table 2). One team combined a photodynamic therapy to the cone resection.The radicality of the procedure (simple cone/trachelectomy or RT) depends both on the tumor response and the team's own conviction. Very few surgical complications were reported (ureteral injury, vessel injury or postoperative bleeding). Few cervical stenoses were reported (Table 2).

Looking at the response, few series reported tumor progression, patients being then ineligible for FSS strategy. Two-thirds of cases had a complete histologic response or a very good response with residual disease in the form of a tumor of a few mm (Table 2). Nevertheless, 25 recurrences (8.3%) were reported, as well as 5 deaths. In stage-IB2 disease, among 131 patients clearly reported with the characteristics of recurrent disease, 16 recurrences (13.2%) were observed. One hundred and thirty-five pregnancies were observed among 112 patients. PR, LBR and PTR rates were respectively 74.5%, 78.7% and 31.5% (Table 3).

3.4. Abdominal radical trachelectomy

Three different abdominal modalities were reported: laparotomy/open, pure laparoscopy or robot-assisted laparoscopy.

3.5. Open RT

Nearly 2200 cases were reported in the literature among 44 series during the past 20 years (Supplementary Table 2) [50,51]. Among them, at least 249 patients were excluded (due either to poor histological features that required a hysterectomy and/or adjuvant therapy, or patients with positive margins). Finally, nearly 1900 cases underwent a successful FSS. There is a trend to preserve uterine artery in the past years and, when reported, the use of a cervical cerclage to decrease the risk of foetal loss is done by nearly all teams (but 3). Regarding uterine artery management, diverse modalities were reported: 1. uterine artery preservation and ligation of the cervico-vaginal branches; 2. ligation the uterine artery; 3. uterine artery ligation, though with a vascular reanastomosis (Supplementary Table 2).

Severe perioperative morbidities were significant (though not reported with the other approaches): nearly 40 deep abscesses or peritonitis or tubo-ovarian abscesses (some requiring repeated laparotomy) were observed. Uterine necrosis had also been reported. Significant orbidities related to the cerclage are also observed (cerclage erosion and cervical stenosis). At least 3 patients required a hysterectomy for amenorrhea or hematometra related to the cervical stenosis.

Concerning the oncological results, 76 recurrences (4%) and 20 deaths were reported. It is not possible to analyse the correlation between LVSI and recurrences rate, because the specific status of recurrent patients concerning this prognostic factor is not frequently reported. Among series reporting clearly initially their tumor stage for stage-IB disease and initial characteristics of recurrent patients, 687 stage IB1 patients were identified. Seventeen, (2.4%) recurred compared to 18

Table 3
Details of the main results of this systematic review according to fertility sparing procedures for cervical cancer.

Number	Simple trachelectomy/ cone resection	Radical Trachelectomy Vaginal approach	Radical Trachelectomy Laparotomy	Radical Trachelectomy Laparoscopy	Radical Trachelectomy Robot	Neoadjuvant Chemotherapy
Patients	649	1977	2153	538	208	337
Patients excluded*	59	258	249	91	14	36
Number of teams reporting series/cases**	23	35	44	27	15	31
Number of published articles/abstracts	33	67	81	32	20	42
IB < 2 cm***	436	1013	687	118	Unknown	113
IB between 2 and 4 cm***	0	101	375	57	Unknown	147
IB > 4 cm	0	3	21	At least 3	1	At least 27
IIA	0	10	At least 19	At least 1	0	At least 11
LVSI****	191	At least 495	At least 227	At least 61	Unknown	Unknown
Recurrences*****	18	86	76	29	9	25
DOD****	1	28	27	2	0	5
Recurrence rate (overall)	18/436:4.1%	86/1669:5.1%	73/1836:4%	29/386:7.5%	10/188:5.3%	25/300:8.3%
Recurrence rate IB < 2 cm	18/436:4.1%	48/1037:4.7%	17/687:2.4%	6/114:5.2%	ND****	ND
Recurrence rate IB 2–4 cm	–	21/101:20.7%	18/375:4.8%	6/57:10.5%	ND	16/131:13.2%
Recurrence rate IB < 4 cm				14/254:5.5%******		
Number of pregnancies	243	689	420	77	79	135
Number of pregnant patients	198	412	339	62	55	112
Pregnancy rate*******	80/142:56.3%	337/574:58.7%	190/527:36%	33/65:50%	53/76:77%	70/94:74.5%
Live birth rate********	161/183:88%	342/481:71%	258/387:66.6%	46/69:66.6%	53/71:74.6%	111/141:78.7%
Prematurity rate*********	31/170:18.2%	145/481:30%	92/320:29%	17/69:24.6%	12/51:23.5%	18/57:31.5%

* Patients excluded for N+, margins +, others reasons depriving them of fertility-sparing management or patients reported exclusively for fertility results. Few series had not reported this number.

** In case of repeated publications by the same team only 1 "series" is retained in this table. Note that 22 series published several approaches in the same paper.

*** Tumor size determined in series without recurrence or with recurrences having characteristics (tumor size, histotype, and LVASI status) fully detailed.

**** LVSI: Lymphovascular space involvement; DOD: Died of Disease: ND: not determined or not possible to be calculated because low number of patiented involved.

***** Recurrences in patients treated conservatively or without (adjuvant) treatment depriving them from their fertility.

****** Recurrence rate in stage IB ≤ 4 cm for patients undergoing mini-invasive approach (laparoscopic pure + robot-assisted).

******* Pregnancy rate determined in series with complete data on the total number of patients attempting to become pregnant and the number of them succeeding.

******** Live birth rate determined in series with complete data about the total number of pregnancies (excepting ongoing pregnancies without outcomes reported) and the number of live births. Ratio between the 2 was then determined.

********* Prematurity rate determined in series with complete data about the number of live birth deliveries and the number of premature deliveries. Ratio between the 2 was then determined.

Table 4
Literature review of laparoscopic radical trachelectomy.

Authors-Years	N cases	Stage Size mm	Histological Subtype	LVSI	Uterine artery preservation	Cerclage	Margins	Other treatment	Complications	Fertility	Outcomes
Pomel 2002 [52]	6	2 IA2, 4 IB1 < 20 mm	5 SCC, 1 ADC	6	Yes in 4	Yes	1 Involved	1 CRT	2 unilateral uterine artery injury	2 pregn. 1 T1 loss 1 term pr.	1 recurrence FU 25 mths
Lee 2003	2	IB1 1 = 26 mm, 1 < 20 mm	2 SCC	NR	2	Yes	Free	No	No	No	NED FU 9, 12 mths
Cibula 2005	1	IB1 8 mm	ADC	NR	No	No	Free	No	No	No	NED at 4 mths
Park 2009 [53]	4	1 IA2, 3 IB1 < 10 mm	4 SCC	NR	No Nerve sparing	Yes in 1	Free	No	No	No	1 recurrence Mean FU 34 months
Martin 2010 [54]	9	2 IA2, 7 IB1 5 to 25 mm	6 SCC, 3 ADC	NR	Yes in 7 Nerve Sparing	Yes	Free .	No	NR	2 pregn. 1 term pr. 1 on-going	1 recurrence I B1 25 mm. Mean FU 28 mths
Kim 2010, Park 2012, 2014 [55]	88/79*,**	4 IA2, 72 IB1 2 IB2, 1 IIA1 26 IB1 > 20 mm	60 SCC, 18 ADC, 1 ASC	12	NR	Yes	Free	9 hysterectomy for margins or parametria + 9 adjuvant chemoth.	1 ureteral + Vena cava injury (converted laparot.) 1 vesico-vaginal fistula	17 pregn. in 13 pts. 4 T1 loss 7 preterm pr. 6 term pr.	9 recurrences 5 IB1 > 2 cm FU 44 months
Wang 2011	1	IA2	SCC	NR	Yes Nerve sparing	Yes	Free	No	No	No	No recurrence FU 14 months
Hong 2011 [56]	4	1 IA2, 3 IB1	SCC	NR	Yes Nerve sparing	Yes	Free	No	No	No	1 recurrence Mean FU 8 mths
Rendon 2012	1	IB1 6 mm depth	ASC	NR	No	No	Free	No	No	No	NED 20 mths
Ebisawa 2013 [57]	56/53*	4 IA1, 52 IB1	42 SCC, 12 ADC, 2 ASC	14	Yes	Yes initially	NR	3 hysterectomy + chemoth. ("high risk pts) 1 adjuvant chemotherapy	2 vessels injury (laparoscopically repaired) 2 cerclage erosion	25 pts. attempting 21 pregn. in 13 pts. (10 spontaneous) 5 T1 loss 2 T2 loss 10 preterm pr. 3 term pr. 4 on-going	1 recurrence DOD FU 60 mths
Kucukmetin 2014 [58]	11/10*	IB1	5 SCC, 6 ADC	3	Yes in 2	Yes	1 Involved	1 hysterectomy (margins +)	1 compartment syndrome	No	No recurrence FU 9 mths
Inthasorn 2014	1	IA2	ACC	NR	Yes	Yes	Free	No	No	No	NED 22 mths
Yoon 2015 [59]	17/16*	3 IA1, 14 IB1 12 > 20 mm	10 SCC, 6 ADC, 1 ASC	5	Yes in 15	Yes	1 Involved	1 hysterectomy (margins +) 4 RCT or RT	No	8 pts. attempt., 1 pregnancy	No recurrence FU 14 mths
Vieira 2015*** [60]	20	3 IA1 LVSI+, 14 IA2, 24 IB1	20 SCC, 20 ADC, 2 ASC	11	In only 2	NR In pts. treated laparosc.	5 Involved	5 hysterectomy (margins +) 3 hysterectomy for complications (1 uterine necrosis, 1 peritonitis, 1 pain) 1 adjuvant treatment	2 lymphocyst 2 cerclage erosion 1 uterine necrosis 1 peritonitis 1 chronic pain 2 urinary tract fistula	7 pts. attempting 3 pregnan in 2 pts. 1 T1 loss 1 preterm deliv. 1 on-going	No recurrence FU 25 mths
Schneider 2015	1	IB1 22 mm	SCC	0	Yes Nerve sparing	NR	NR	No	Ureteral fistula	NE	Recurrence 11 mths DOD
Kyrgiou 2015	1	IB1 10 mm in pregnant pt. (14 WG)	ADC	0	Yes	Yes	Free	No	No	During pregnancy	Delivery at 36 WG
Yi 2015	1	IB1 35 mm in pregnant pt. (18 WG)	ADC (mucinous)	0	Yes	No	<5 mm	Adjuvant chemotherapy	No	During pregnancy	Delivery at 32 WG No recurrence at 12 months
Api 2016	1	IB1 25 mm	ADC	0	Yes	No	Free	No	No	No	NED 22 mths
Yoo 2016 [61]	12	2 IA2, 9 IB1 (1 > 2 cm), 1 IB2	8 SCC, 3 ADC, 1 ADS	6	Yes	Yes	Free	1 adjuvant chemotherapy 1 hysterectomy (suspicion recurrent disease)	1 bleeding requiring a second laparoscopic surgery	4 attempting 2 pts. had 2 pregnancy (IVF) 2 Preterm delivery	No recurrence FU 51 mths

(continued on next page)

Table 4 (*continued*)

Authors-Years	N cases	Stage Size mm	Histological Subtype	LVSI	Uterine artery preservation	Cerclage	Margins	Other treatment	Complications	Fertility	Outcomes
Saadi 2015, 2017 [62]	22	5 IA2, 17 IB1 (16 < 20 mm)	17 SCC, 5 AD	10	Yes in 18 No in 4	Yes	Free	No	2 lymphocysts, 1 cervical stenosis 1 Asherman syndrome	2 pregnancies (1 term & 1 peterm delivery)	2 recurrences 2 stage IB1 < 20 mm FU 16 mths
Balaya 2019 [63] Multicenter trial	4	No specific report	No specific report	NR	NR	NR	NR	NR	4 morbidities not detailed	No specific report	No specific report
Lu 2013, 2014, 2019 [64]	46****	33 IB < 20 mm, 13 IB ≥ 20 mm	43 SCC, 3 AD	2	Yes	Yes	Free 1 Parametria +	2 adjuvant chemotherapy	2 lymphocyst 1 Pelvic infection Urinary retention 2 urinary infection	12 pts. attempt., 9 pregn. in 9 pts. 3 T1 loss 1 preterm pr. 1 term pr. 3 on-going**** 9 pregnancies (7 spontaneous)	No recurrence FU 80 mths
Chernyshova 2020 [65]	39	No specific report	No specific report	NR	NR	Yes	No	NR	No cervical stenosis	5 T1 loss, 1 T2 loss 2 preterm and 1 term delivery	2 recurrences but approach unclear
Machida 2020, Iwata 2021 [50,66] Multicenter study	29*****	No specific report	No specific report	NR	NR	NR	NR	NR	NR	6 pregnant pts	No specific report
Salvo 2021 [51] Multicenter study	121	No specific report	No specific report	NR	NR	NR	NR	NR	NR	NR	9 recurrences
Kanao 2021[128]	40/35*	8 IA2, 29 IB1, 3 IIA1	29 SCC, 11 AD	NR	Yes	Yes	4 positive	10 adjuvant chemotherapy 5 hysterectomy	1 peritonitis 1 internal hernia	9 pts. attempting 7 pts. having 9 pregnancies 8 live birth 1 T1 loss	1 recurrence FU 40 mths

SCC: Squamous Cell Carcinoma; ADC: Adenocarcinoma; ADS: Adenosquamous Carcinoma; CRT: Chemo- Radiation Therapy; ERT: External Radiation Therapy; LVSI: Lympho-Vascular Space Involvement; N+ Nodal involvement.
T1: First trimester of the pregnancy; T2: Second trimester of the pregnancy; NR: Not Reported; FU: Follow-up; NED: No Evidence of Disease; DOD: Died of Disease. All FU times are given as medians except when the mean is stated.
Recurrences reported are observed in patients treated without adjuvant treatment depriving her fertility potential.

* :The initial figure concerns patients scheduled for fertility sparing management (FSM) and the second one, patients who finally underwent FSM.
** : 6 patients received neoadjuvant chemotherapy in the series presented in 2012.
*** : The paper reported 20 cases using the pure laparoscopic approach but the data are mixed with the minimally-invasive robot-assisted procedure in the rest of the current table.
**** : 13 pts. receiving neoadjuvant chemotherapy; fertility results being reported in the series published in 2014.
***** : laparoscopic trachelectomy including laparoscopic-assisted surgery.

out of 375 (4.8%) patients having stage IB2 disease ($p < .05$). Four hundred and twenty pregnancies were reported in 339 patients. PR, LBR and PTR were respectively 36%, 66.6% and 29% (Table 3).

3.6. Minimally-invasive RT (laparoscopic or robotic)

These procedures are more recent (since 2002 for the first laparoscopic pure RT [52,67], and 2008 for the robot assisted laparoscopic approach) (Table 4 & Supplementary Table 3). Among 538 cases are reported using laparoscopic pure strategy (in 27 series), 91 cases were excluded due to unfavourable prognostic factors. One hundred and eighteen patients had stage-IB1 disease and 57 a stage-IB2 disease. Twenty-nine recurrences (7.5%) were observed, as well as 2 deaths. Correlating tumor stage and recurrence rate, 5.2% of recurrence were observed in stage-IB1 disease compared to 10.5% in stage-IB2 lesions. We should however take these rates with caution since the number of series reporting in details their tumor stages distribution and characteristics of recurrent patients is limited (respectively only 114 and 57 stages IB1 and IB2 diseases). Seventy-seven pregnancies had been reported in 62 patients. PR, LBR and PTR are respectively 50%, 66.6% and 24.6% (Table 3). Little major morbidity was reported.

Concerning the robotic approach, 208 cases were reported in 15 teams, with 14 patients being excluded (Supplementary Table 3). If we except the multicentre study of Salvo et al. [51], only one group published more than half of the cases. As cases from Sweden and US are included in the very recent Salvo et al. study, recurrent rates were evaluated taking account the said Salvo et al. study, and not the other teams included in this Salvo et al. [51]. It is not possible to calculate the recurrence rate according to disease stage or tumor stage, because we do not have the initial characteristics of recurrent patients (particularly between stage-IB1 or IB2 disease). Seventy-nine pregnancies were observed in 55 patients. PR, LBR and PTR were respectively 77%, 74.6% and 23.5% (Table 3).

Comparing the recurrence rates according to the surgical approaches (laparotomic *versus* mini-invasive surgery) in patients having stage-IB 1 & 2 diseases (similarly to the inclusion criteria of the LACC trial), among 1065 patients undergoing a laparotomic RT, 35 recurrences (3.3%) were observed compared to 14 (5.5%) among 254 having a mini-invasive approach (laparoscopic or robot-assisted)(NS). PR and LBR in this last group are respectively 59.8% and 69.4% (Supplementary Fig. 2).

4. Recurrent rates in stage-IB1 and IB2 diseases (Figs. 1 & 2)

Fig. 1 focuses on the recurrence rates observed according to 4 approches: simple cone/trachelectomy, VRT, RT by laparotomic and pure laparoscopic. We had not evaluated the recurrence rate in stage-IB1 disease after NACT, because oncologic rationale to expose patients to chemotherapy in a small tumor size is really questionable. RT by robot-assisted laparoscopic approach was not included, because of a lack of specific data in this subgroup of patients with smaller tumor sizes. PR and LBR were added in this figure, but determined for the entire population of patients undergoing these approaches. The lower rate of recurrence is observed in patients undergoing the laparotomic approach (2.4% *versus* respectively 4.1%, 4.7%, and 5.2% for simple cone/trachelectomy, VRT and RT laparoscopic approach). On the other hand, the lower PR is also observed in patients undergoing an open approach.

Fig. 2 focuses on tumor sizing between 20 and 40 mm. As the VRT is a non-acceptable approach in this context, we compared NACT and RT by laparotomic and laparoscopic approaches. The rate observed in the group of patients treated by laparoscopic approach should be taken with a great caution, because few patients are involved ($n = 57$). The rates of recurrence is significantly higher after NACT compared to laparotomic approach (13.2% *versus* 4.8%; $p = .001$).

5. Discussion

During the last 2 years, several high quality (systematic) reviews or meta-analyses have been published on fertility sparing strategies in cervical cancer [7–13]. Two of them concerned patients undergoing NACT followed by conservative treatment for tumors >20 mm, but without evaluation of other procedures to compare the oncologic results [11,12]. Others focused exclusively on results of the 3 approaches to perform RT (vaginal, open and laparoscopic), without integrating cone/simple trachelectomy or NACT [9]. And others involved different strategies, but without NACT, and mixing pure laparoscopic and robot-assisted laparoscopic RT [10]. Several of them had incorporated in analysis and tables, data reported by the same team at different period (redundant/duplicating results or addition of the same patients in the total number) [7,10–12]. Others still integrated only series involving >10 patients treated, to reinforce the sturdiness of their analysis, though taking the risk of the omission of contributive information contained in smaller series [13]. In the current review, we use the same methodology that we

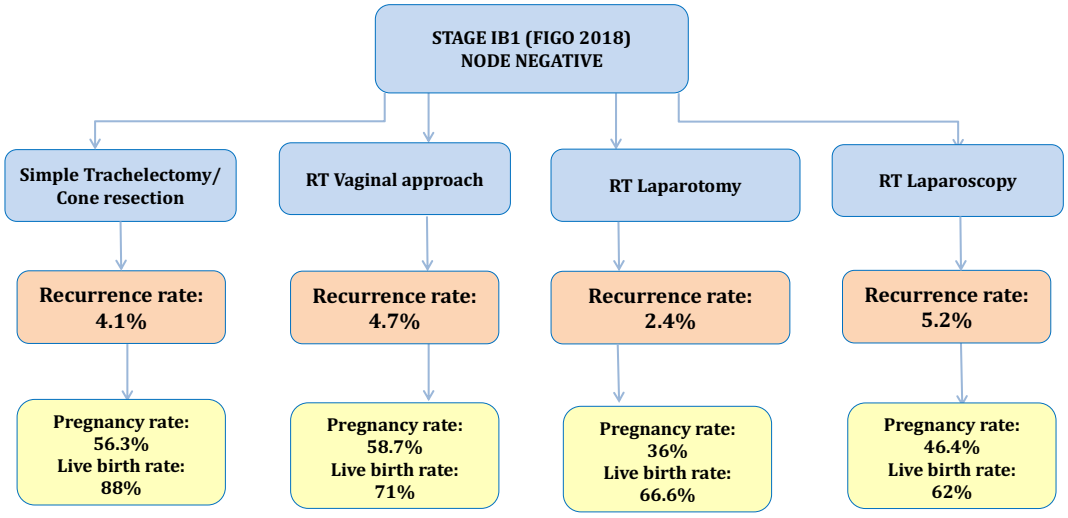

Fig. 1. Results of fertility-sparing strategies in stage-IB1 (FIGO 2018) cervical cancer (RT = Radical Trachelectomy). Pregnancy and life birth rates are determined for the entire population and not specifically for stage-IB1 disease.

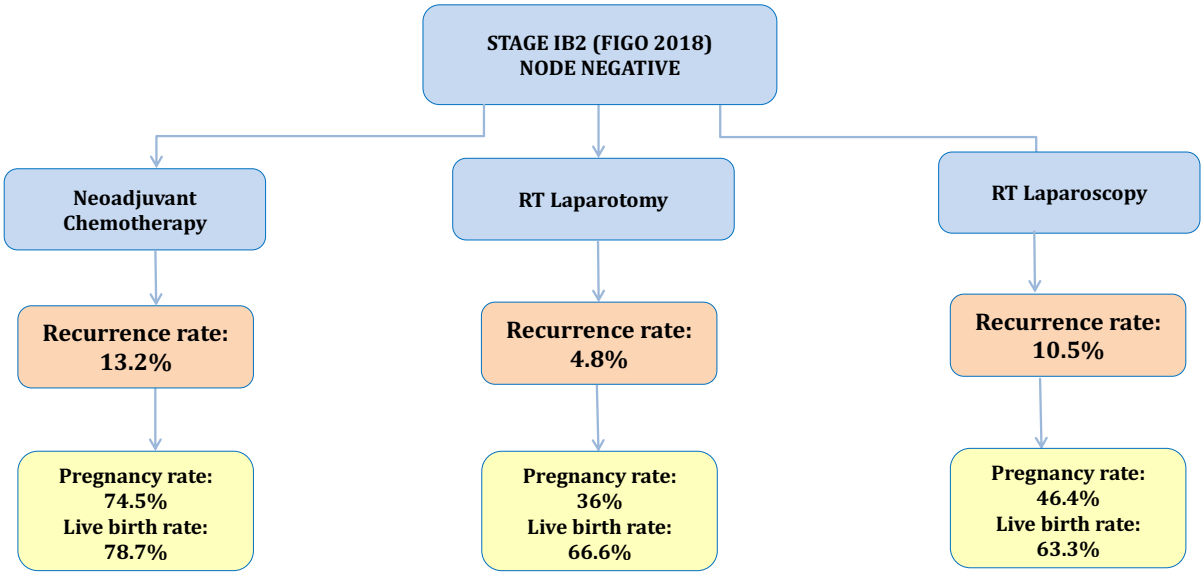

Fig. 2. Results of fertility-sparing strategies in stage-IB2 (FIGO 2018) cervical cancer (RT = Radical Trachelectomy).

defined several years ago: a systematic review integrating also case report(s) and very small series (having at least >12 months of follow-up) and screaning all authors/institution to avoid counting twice duplicate series at different periods by the same institution. But our methodology (as all the others used for similar systematic reviews) has also weaknesses such as comparing series with different inclusion criteria, varied skilling of teams, sometimes very few information about pathologic criteria (LVSI status, and depth of stromal invasion, for exemple), lengths of follow-up, follow-up procedures used… Nevertheless, the criteria that we defined to include papers seemed to us the most suitable ones to compare the 5 strategies that are currently used to promote fertility in early-stage cervical cancer, and also to allow opportune comparisons with what we reported 6 years ago.

The results currently reported change drastically compared to what we concluded previously. This is related to the number of cases reported combined with a longer follow-up in older series. We globally doubled, or tripled in some strategies, the number of cases analysed, increasing then from nearly 3000 to 6000 patients selected for FSS (Table 3). Impacts are sometimes major: for example in simple cone/trachelectomy, a single ambiguous recurrence was reported 6 years ago, *versus* 18 patients in the current analysis (Table 1). FSS, whatever the strategy used, should be offered to young patients with conventional histotype (squamous carcinoma, adenocarcinoma or adenosquamous lesion) and the most favourable prognostic factors (no extracervical disease) treated by exclusive surgery. But how can we move forward and define the best candidates for each procedure on the basis of accurate and reproducible criteria?

As it has been stated recently very appropriately by Machida et al., definition of ideal candidate should integrate a combination of 3 criteria related to the tumor size, the depth of stromal invasion and the LVSI status [50]. These criteria, particularly the last 2, are accurately determined after the full pathologic examination of the cervix. Does it mean that, before deciding the optimal strategy, a cone biopsy should be systematically performed (if not done previously to define the malignancy) to stadify patients as precisely as possible [68]? On the other hand, this strategy, implying at least 2 cervical resections, will then have a potential deleterious impact on the fertility results by shortening the length of the uterine corpus. Furthermore, do we need to have such a cone biopsy in patients with stage-IB2 disease? Surely not, particularly in cases of macroscopically visible lesion! Among the 3 factors previously mentioned, the sole one that could be known before surgery, and with a relative accuracy, using the clinical examination combined with imaging (MRI +/− ultrasonography by expert radiologist) is the tumor size [2]. This is why, to evaluate the results and decide then between each strategy, discussion is mainly organised according to this accessible criterion (Figs. 1 and 2).

For patients with the most favourable prognosis (stage-IB1 disease), the use of a simple conisation/trachelectomy had been more widely reported in recent series during the last 2 years. In 2016, we evaluated the recurrence risk <0.5%, but since then, and after reviewing the last reports, this rate is henceforth more accurately evaluated to 4.1% (Table 3). Can we evaluate this rate in patients without LVSI? It is not possible to calculate this rate in the current analysis, because very few series reported their complete initial data of stage-IB1 disease (including LVSI status) and recurrent disease. Nevertheless, we can observe that at least 6 of recurring stage-IB1 patients had no LVSI initially (Table 2). In the recent publication of the major CONCerv trial, involving patients without LVSI, among 31 patients with stage-IB1 disease treated with simple cone/trachelectomy, 1 (3%) recurred locally (data from K. Schmeler [33]). This rate is then "robust". It is not "0%", and so this risk of recurrence of 1/30 should then be exposed to patients before suggesting such a strategy. The ongoing GOG 278 trial (including patients treated with simple cone/trachectomy and simple hysterectomy) will probably improve information about the quality of life of such management (NCT01649089). Anyway, the paper from Tomao et al. adds also interesting data in this regard [24]. The risk of recurrence of the conisation/simple trachelectomy (even if theoretically these procedures are "easy") is decreased when patients are treated in centers skilled to such strategy. This raises the following twofold question: the length of free margins, particularly in stage-IB1 disease (with the complex compromise between the length of free margins and the balance between the size of the remaining uterus), and the quality of pathologic analysis of surgical specimens. This paper is then a strong plea for the centralization of cases eligible for FSS in "referent" centers really skilled to these strategies, even when a simple cone/trachelectomy is planned [24]. Unfortunately we have no specific data about the learning curve required for each procedure. In the open RT, particularly ligating the uterine arteries, the technique is very comparable to the radical hysterectomy procedure. But this learning curve effect is probably more impoprtant in mini-invasive, vaginal approaches or with open RT with uterine arteries preservation, probably well over 20 cases.

The VRT collects now nearly 2000 cases. It requires really skilled surgeons to the vaginal route (less tought in recent years). So, its use trends to decrease to the benefit of abdominal approaches or simple cone/

trachelectomy (Table 3). Nevertheless, collecting additional cases, our analysis shows a consistent rate of recurrence well indentified for 10 years (about 5%) and significant fertility results (Supplementary Table 1). An increased rate of recurrence is observed in patients with tumor size >20 mm reaching then a nonacceptable rate of recurrence of 20.7% (Table 3). This is a clear limit to the safety of this procedure. But in the current analysis, unlike what we reported 6 years ago, the LVSI status does impact significantly the recurrence rate. Conventional patients with LVSI, being in the group of patients having "intermediate risk factors", are not eligible for FSS. But on the other hand, if we summerized all papers published, nearly 1000 patients undergoing FSS with LVSI were reported (including anyway some cases of stage IA diseases)(Supplementary Table 3). Indeed, the pathologic recognition of LVSI is sometimes complex. But a recent and very interesting paper from the Roman group of Scambia et al. suggests the use of a semi-quantitative evaluation of LVSI (negative *versus* focal *versus* diffuse) to better evaluate the prognostic impact of this factor [69]. This is an interesting option, because if FSS is clearly contra-indicated in patients with diffuse LVSI, similar to lymphangitis (requiring then an adjuvant treatment), such a conservative strategy could be probably considered in patients with stage-IB1 disease and focal LVSI (having in the Ronsini et al. paper the same prognosis than patients without LVSI) [69]. If so, what should then be the best strategy in patients with focal LVSI: simple cone/trachelectomy, a VRT or a RT by abdominal approach? The depth of stromal invasion (< or >10 mm and/or < or >2/3 of the cervical stroma) should probably be also integrated; still, we have no sufficient data to answer this question. Our analysis suggests nevertheless that such a situation may be potentially the sole remaining indication of the use of a vaginal approach to perform RT.

In the stage-IB1 disease group of patients, the lower rate of recurrence is observed in patients treated with laparotomic approach for RT (2.4%). Still, we can also observe that PR is the worst in this subgroup. Is it due to the use of a laparotomic approach (with an increased rate of septic severe morbidities and postoperative adhesions), or to the ligation of uterine arteries, both factors having potentially a negative impact on the fertility potential? On the other hand, the previous publication analysed 6 years ago shows that only 175 pregancies were observed in patients undergoing a RT by laparotomic approach, compared to 420 in the current analysis last one (Table 3). Increasing time of follow-up could increase this rate in the future. One option to reduce the risk of peritoneal trauma, which could induce adhesions and deep sepsis and then decrease the fertility results, is the use of a mini-invasive approach. PRs observed after laparoscopic pure and robot-assisted mini-invasive approaches are higher compared to what is observed after the use of a laparotomic approach (Table 3). However, following the LACC trial demonstrating a deleterious impact of the use of a mini-invasive approach compared to laparotomy on survivals for stage-IB1 and 2 cervical cancer patients undergoing radical hysterectomy, our analysis is quite reassuring for patients treated using FSS. These results are in the same lines as the recent results from the International radical trachelectomy assessment/IRTA study demonstrating no deleterious effect of the use of a (robot-assisted) laparoscopic surgery to carry out a RT [51]. So clearly, such mini-invasive approach could be a good compromise to the laparotomic one for patients for stage-IB1 with "intermediate" risk group (for exemple focal LVSI). A randomized trial is ongoing in China comparing both strategies (2 arms: 1 laparotomy and 1 mini-invasive with 2 approaches allowed: laproscopic pure or robot-assisted one) and will help to clarify their respective results [70].

The last important results raised in the current paper pertain to the optimal management of patients with tumor size >20 mm. As we have very limited data of such FSS in patients with tumor size >40 mm and/or stage-IIA diseases (requiring a higher rate of adjuvant treatment based on intermediate or high risk group), it is impossible to evaluate its safety. We then continue to consider these situations as contra-indication to the use of FSS. So, what is the best strategy for stage-IB2 disease between 20 and 40 mm? The number of stage IB2 disease undergoing a laparoscopic RT is very small (57 patients), it is then not possible to accurately evaluate the oncological results of such approach in patients having a tumor size between 20 mm and 40 mm. Even more, this rate could not be evaluated in patients treated using a robotic approach, due to a lack of specific report for this subgroup of patients, whereas the use of a robot-assisted laparoscopic approach to carry out a RT is increasing. The 2 most reported procedures in this context are NACT followed by conservative approach and Open RT. Our current analysis demonstrated a risk of recurrence of 13.2% in patients undergoing NACT in stage-IB2 disease, drastically increased (the double) compared to what we observed 6 years ago [5]. More cases added, more recurrences reported, particularly during the last 3 years… Just to remind that the 4.5 year-DFS in patients treated radically with open surgery for tumor stage <40 mm was 96.5% in the recent LACC trial… [1]. Nevertheless, these results should be taken with caution, NACT is a very heterogeneous group in terms of combination of drugs used, number of courses of neoadjuvant chemotherapy, criteria to evaluate the response before the surgery, criteria to define the radicality of the surgery…a very long list that could be confusional factors. On the others hands our data are quite close to the results of 2 recent review specifically dedicated to this topic [11,12]. Prospective trial or observational studies could be very helpful to have a better view of the oncologic results of such strategy, particularly in tumors >20 mm. Two observational trials are ongoing, one in China integrating stage-IB1 and IIA diseases (SYSUGO-005/CSEM009 trial NCT02624531) and the NEO-CON-F/CONTESSA trial dedicated exclusively to stage-IB2 disease, involving 90 patients (NCT04016389) [71]. What should be then the comparative group to evaluate the "safety or unsafety" of NACT? What should be then the "non-acceptable" rate of recurrence to consider NACT for stage-IB2 disease as unsafe, if so?

While waiting for the results of these studies, we can nevertheless observe that the use of NACT increased significantly the risk of recurrences compared to open RT suggesting that this later strategy is oncologically the best choice. Having said that, these "worst" results should be put in mirror of the fertility results with, as we stated previously, a decreased PR in patients treated by a laparotomic approach. Better oncologic results, but with lower fertility results… This observation comparing NACT to open RT in stage-IB2 diseases summerizes perfectly the difficulties and challenges about the evaluation of the results of FSS in early stage cervical cancer, as well as its paradox.

Contributors

Designing the study: PM, SG
Extracting the data: All authors
Analysing the results: PM, SG, AL, PP, CG, MG
Approval of the manuscript: All authors

Conflict of interest

The authors have no conflict of interest related to this manuscript.

Funding

No sources of funding for the current systematic review. No authors are employed by NIH.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2022.01.023.

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