



HAL
open science

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

P. Morice, A. Maulard, S. Scherier, C. Sanson, J. Zarokian, F. Zaccarini, S. Espenel, P. Pautier, A. Leary, C. Genestie, et al.

► To cite this version:

P. Morice, A. Maulard, S. Scherier, C. Sanson, J. Zarokian, et al.. Oncologic results of fertility sparing surgery of cervical cancer: An updated systematic review. *Gynecologic Oncology*, 2022, 165 (1), pp.169-183. 10.1016/j.ygyno.2022.01.023 . hal-04514133

HAL Id: hal-04514133

<https://hal.science/hal-04514133>

Submitted on 22 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

ONCOLOGIC RESULTS OF FERTILITY SPARING SURGERY OF CERVICAL CANCER: AN UPDATED SYSTEMATIC REVIEW

Morice Ph.^{1,2,3}, Maulard A.¹, Scherrier S.¹, Sanson C.¹, Zarokian J.¹,
Zaccarini F.¹, Espenel S.⁴, Pautier P.⁵, Leary A.^{5,6}, Genestie C.⁷,
Chargari C.^{2,4}, Grynberg M.^{3,8}, Gouy S.¹

1. Department of Gynecological Surgery, Gustave-Roussy, Villejuif, France
2. Inserm Unit 10-30, Gustave-Roussy, Villejuif, France
3. University Paris-Sud (Paris XI), Le Kremlin-Bicêtre, France
4. Department of Radiation Oncology, Gustave-Roussy, Villejuif, France
5. Department of Medical Oncology, Gustave-Roussy, Villejuif, France
6. Inserm Unit 981, Gustave-Roussy, Villejuif, France
7. Department of Pathology, Gustave-Roussy, Villejuif, France
8. Department of Reproductive Medicine, Hôpital Antoine-Béclère, Clamart, France

Running title: Conservative treatment of cervical cancer

Address correspondence to:

Philippe Morice – Department of Gynecological Surgery, Gustave-Roussy Cancer Campus,
114 rue Édouard-Vaillant, 94805 Villejuif Cedex, France.

Phone: 33142114439 – Fax: 33142115213 – Email: philippe.morice@gustaveroussy.fr

50 **Abstract**

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

55 **Results:** Data were identified from searches of MEDLINE, Current Contents,
56 PubMed and from references in relevant articles from January 1987 to 15th of
57 September 2021. We carry out an updated systematic review involving 5,862 patients
58 initially selected for fertility-sparing surgery in 275 series.

59 **Findings:** In patients having a stage IB1 disease, recurrence rate/RR in
60 patients undergoing simple conisation/trachelectomy, radical trachelectomy/RT by
61 laparoscopico-vaginal approach, laparotomic or laparoscopic approaches are
62 respectively: 4.1%, 4.7%, 2.4% and 5.2 %. In patients having a stage IB2 disease, RR
63 after neo-adjuvant chemotherapy or RT by laparotomy are respectively 13.2% and
64 4.8% (p=.0035). After neoadjuvant treatment a simple cone/trachelectomy was carried
65 out in 91 (30%) patients and a radical one in 210 (70%) cases. But the lowest
66 pregnancy rate is observed in patients undergoing RT by laparotomy (36%).

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

73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95 **Key words:** early-stage cervical cancer, conservative treatment, conisation,
96 trachelectomy, neoadjuvant chemotherapy, fertility, prognostic factor, radical
97 trachelectomy, recurrence.

99 **Introduction**

100
101 Prognostic factors of early stage cervical cancer are clearly identified: tumor size
102 (related to the 2018 FIGO staging system with a cutoff at 20 and 40 mm), the nodal
103 status, the lympho-vascular space involvement status (LVSI), the depth of stromal
104 invasion and, more recently, as showed in a large randomized trial with unexpected
105 results, the surgical approach [1-3]. The standard surgery comprises then a
106 hysterectomy combined with nodal staging surgery that could be a full pelvic
107 lymphadenectomy or a selected nodal dissection with sentinel lymph node (SN) biopsy,
108 currently evaluated in several trials over the globe [2].

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

128 Five years ago, we published a full review of the literature dedicated to oncologic
129 issue and fertility issues after FSS [5,6]. The key messages of these papers, with the
130 knowledge of the literature from the mid 2010s, were firstly to report a very low
131 recurrence rate in patients treated with simple cone/trachelectomy (a single ambiguous
132 recurrent disease reported at that time), validating then this concept. Furthermore, VRT
133 procedure is “safer” in patients with tumor size < 20 mm, but with no statistical difference
134 in terms of recurrence, in patients with LVSI. At last, in case of patients with tumor size
135 between 20 and 40 mm (current stage IB2 according to the 2018 FIGO classification³),
136 the preferred strategy should be NACT instead of RT by laparotomic approach (similar
137 rate of recurrences, but higher fertility results in the first option)[5,6].

138 Since that date, many reviews and/or meta-analysis have been published (just for
139 the last months [7-13]). Criteria to select papers in these reviews were different from one
140 to the other, adding sometimes in one calculation cases and data from the same
141 institution, but published at different periods. Impacts of these papers to choose between
142 the 6 previous strategies in 2021 remain unclear. As many papers and new series had
143 been published during the past few months, we decided to update our previous review

144 with the same methodology that we used initially, which required to perform a systematic
145 review and analysis of all published series and case reports in order to try to use the
146 results obtained to measure accurately the recurrences rates, fertility results and then
147 define the potential indication for each procedure used for FSS. The first aim of this
148 update review is then to clarify the oncologic outcomes for each procedure and thereafter
149 to discuss their fertility results.

150

151 **Data collection**

152

153 Search strategy and selection criteria

154 Data were identified from searches of MEDLINE, Current Contents, PubMed
155 and from references in relevant articles from 1987 to September 15, 2021, using the
156 following search terms: “early-stage cervical cancer”, “conservative surgery”,
157 “conservative treatment”, “fertility-sparing surgery”, “trachelectomy”, “radical
158 trachelectomy”, “laparoscopic trachelectomy”, “laparot* trachelectomy”, “robot*
159 trachelectomy”, “abdominal trachelectomy”, “neoadjuvant chemotherapy”, “conisation”
160 and “cone resection”. Only articles published in English, or having a detailed abstract
161 in English, were included. The series comprising the largest number of patients (or the
162 most complete data) was retained for repeated publications by the same team, We
163 excluded the specific management of paediatric tumors. Papers exclusively focused on
164 a technical description without any follow-up > 12 months (if no intercurrent event
165 reported in the paper-meaning pregnancy or recurrence) were not included (excepting
166 in the case of a new procedure described for the first time). Pure reviews of the
167 literature and analyses of national cancer registry or epidemiologic database having
168 insufficient data to study precise specific characteristics of recurring patients, were not
169 included in the current analysis. The design of this systematic review of the literature is
170 done in accordance with the PRISMA guidelines. The PRISMA flow diagram detailing
171 the selection and exclusion criteria of papers is presented in Supplementary Figure 1.

172

173 Analysis

174 The first and the last authors extracted and analysed the different series. The
175 main issue of this review is to focus on the oncologic outcomes. The analysis
176 comprises the patients’ characteristics (tumor size, stage, histological subtype, LVSI
177 status, depth of stromal invasion, and margins status if known), specific surgical
178 aspects (approach, preservation or not of the uterine artery, cerclage...), major
179 morbidities (related to the lymphadenectomy and the cervical procedure) and
180 characteristics of recurrent disease. Concerning the FIGO staging system, we
181 integrate the FIGO classifications used in publications. However, regarding the most
182 simple procedure (simple conisation/trachelectomy) -as the key issue is to evaluate
183 the results of FSS for invasive carcinoma- we excluded papers involving only stage-IA
184 disease. We then try also to convert into 2018 FIGO staging³ whenever possible
185 (Table 1). The overall survival could not be studied, since we had very few data about
186 the long-term outcomes of recurring patients after such strategies, explaining then the
187 wide discrepancy between number of recurrences and number of deaths.

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

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

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

219 Findings

221 Vaginal RT

222
223 We begin by this procedure that is historically the first one reported. Table 1 of
224 the supplementary materials details the series devoted to VRT [4]. About 2,150 cases
225 were reported by more than 35 teams. At least 250 patients have been excluded (few
226 series had not mentioned this figure), on the basis of intermediate or poorer prognostic
227 factors, because they had finally received an adjuvant treatment or had undergone a
228 completion hysterectomy (mainly for positive margins)(Supplementary Table 1)[4].

229 A majority of patients had stage-IB (FIGO 2018) disease, but few stage-IIA1
230 were included. A majority of stage-IB1 tumors measured $<$ 20 mm, but at least 101
231 cases had stage-IB2 lesions $>$ 20 mm; were observed (reporting their outcomes).
232 Peroperative morbidities were scarcely reported: several cases of bleeding or vessel

233 injuries or urinary tract injuries (> 30 cases). The main postoperative morbidities were
234 related to the lymphadenectomy and were observed with all types of FSS
235 (lymphocysts and lymphoedema) or related to the cerclage used by a majority of
236 teams after removing the cervix (cervical stenosis and cerclage erosion).

237
238 Among 1,904 patients who finally underwent FSS (by definition node-negative
239 cases), 86 recurrences and 27 deaths were observed. Three recurrences were
240 reported in patients with a small neuroendocrine tumor. The recurrence rate is 5.1%.
241 Two main factors for recurrence were analysed: the tumor size (< or > 20 mm) and
242 LVSI status. In series reporting clearly the tumor size and characteristics of their
243 recurrent disease (if observed), among 1,037 patients having stage IB1 disease 48
244 (4.7%) recurrences were observed, *versus* disease 21/101 (20.7%) for stage IB2 ($p <$
245 $.00001$). Concerning the impact of LVSI status (independently from disease stage), the
246 recurrences rates were respectively in patients with or without LVSI 14/592 (2.4%) and
247 19/266 (7.1%) ($p < .001$). But we do not have data about the impact, according to the
248 number of LVSI foci, their location (inside the tumor or around it) and their type
249 (vascular or lymphatic). PR, LBR and PRT were respectively 58.7%, 71% and 30%.

250
251 Patients with a stage-IB1 tumor \leq 20 mm: a simple trachelectomy or conisation

252
253 Table 1 shows all the cases of such management in stage-IB1 disease: 649
254 patients were published by 23 different teams (Table 1)[14-33]. As we mentioned
255 previously, all papers reporting exclusively the management of stage-IA disease were
256 excluded, but in scarce series reported in the current table focusing on stage-IB
257 disease, few stages-IA disease were mixed to stage IB1, and discrimination of specific
258 results for invasive carcinoma is difficult. Logically, all of them reported a tumor size \leq
259 20 mm. All patients underwent a pelvic lymph node dissection (total pelvic
260 lymphadenectomy or sentinel node dissection). Nearly 60 patients were excluded
261 because of nodal involvement. Nearly 200 cases had LVSI. All cervical resections
262 were done using a vaginal approach, except one team using an abdominal approach
263 [23].

264
265 Eighteen (4.1%) recurrences were observed (in patients treated successfully for
266 this conservative management) and 1 death was reported. The location of the
267 recurrent disease was: cervix in 12 patients, nodal in 4, ovarian in 1, and parametria in
268 1. It is impossible to evaluate accurately the risk of recurrence according to LVSI
269 status (because very few series reporting the LVSI status in stage lesion and specified
270 as initial prognostic factor in recurring cases). But interestingly, among recurrent
271 patients, 6 had initially LVSI, 6 had not, and this status is unknown in 6 others. PR,
272 LBR and PRT were respectively 56.3%, 88% and 18.2%.

278 Neoadjuvant chemotherapy (NACT) followed by conservative surgery

279
280 Table 2 summarizes all the cases reported on NACT [21,22,34-49]. Amongst
281 the 337 cases reported that were selected for this management, 301 underwent
282 eventually uterine conservation. Simple cone/trachelectomy (by vaginal approach
283 except in one team using abdominal approach) was carried out in 91 (30%) patients
284 and a radical one in 210 (70%) cases (vaginal, open or mini-invasive)(Table 2). A
285 majority of patients had stage-IB1 or 2 diseases, but at least 51 and 11 had a stage-
286 IB3 or IIA disease. Amongst patients with stage-IB1 and 2 diseases, 113 had a tumor
287 size < 20 mm, and 147 between 20 and 40 mm. A majority of patients received 3
288 courses of platinum-based chemotherapy. Three teams administered direct intra-
289 arterial (intrafemoral or intra-uterine artery) chemotherapy combined in one with
290 intravenous chemotherapy. Chemotherapy combined initially 3 drugs (in majority:
291 platinum based, paclitaxel and ifosfamide) in the initial years, but during the last 5 to 10
292 years, 2 drugs only were used (carbo or cisplatin and paclitaxel). Chemotherapy
293 toxicities were moderate and manageable (mainly haematological).

294 Concerning the surgical approach reported to remove the cervical disease, a
295 majority of teams used a vaginal approach, a laparoscopic approach (4 teams), a
296 robotic one (1 team) and even a laparotomic one (7 teams)(Table 2). One team
297 combined a photodynamic therapy to the cone resection. The radicality of the
298 procedure (simple cone/trachelectomy or RT) depends both on the tumor response
299 and the team's own conviction. A simple cone/trachelectomy was carried out in 91
300 (30%) patients and a RT in 210 (70%) cases. Very few surgical complications were
301 reported (ureteral injury, vessel injury or postoperative bleeding). Few cervical
302 stenoses were reported (Table 2).

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

311
312

313 Abdominal radical trachelectomy

314

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

317

318 Open RT

319 Nearly 2,200 cases were reported in the literature among 44 series during the
320 past 20 years (Supplementary Table 2)[50,51]. Among them, at least 249 patients
321 were excluded (due either to poor histological features that required a hysterectomy
322 and/or adjuvant therapy, or patients with positive margins). Finally, nearly 1,900 cases

323 underwent a successful FSS. There is a trend to preserve uterine artery in the past
324 years and, when reported, the use of a cervical cerclage to decrease the risk of foetal
325 loss is done by nearly all teams (but 3). Regarding uterine artery management, diverse
326 modalities were reported: 1. uterine artery preservation and ligation of the cervico-
327 vaginal branches; 2. ligation the uterine artery; 3. uterine artery ligation, though with a
328 vascular reanastomosis (Supplementary Table 2).

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

335
336 Concerning the oncological results, 76 recurrences (4%) and 20 deaths were
337 reported. It is not possible to analyse the correlation between LVSI and recurrences
338 rate, because the specific status of recurrent patients concerning this prognostic factor
339 is not frequently reported. Among series reporting clearly initially their tumor stage for
340 stage-IB disease and initial characteristics of recurrent patients, 687 stage IB1 patients
341 were identified. Seventeen, (2.4%) recurred compared to 18 out of 375 (4.8%) patients
342 having stage IB2 disease ($p < .05$). Four hundred and twenty pregnancies were
343 reported in 339 patients. PR, LBR and PTR were respectively 36%, 66.6% and 29%
344 (table 3).

345 Minimally-invasive RT (laparoscopic or robotic)

346 These procedures are more recent (since 2002 for the first laparoscopic pure
347 RT [52,67], and 2008 for the robot assisted laparoscopic approach)(Table 4 &
348 Supplementary Table 3). Among 538 cases are reported using laparoscopic pure
349 strategy (in 27 series), 91 cases were excluded due to unfavourable prognostic
350 factors. One hundred and eighteen patients had stage-IB1 disease and 33 a stage-IB2
351 disease. Twenty-nine recurrences (7.5%) were observed, as well as 2 deaths.
352 Correlating tumor stage and recurrence rate, 5.2% of recurrence were observed in
353 stage-IB1 disease compared to 10.5% in stage-IB2 lesions. We should however take
354 these rates with caution since the number of series reporting in details their tumor
355 stages distribution and characteristics of recurrent patients is limited (respectively only
356 114 and 57 stages IB1 and IB2 diseases). Seventy-seven pregnancies had been
357 reported in 62 patients. PR, LBR and PTR are respectively 50%, 66.6% and 24.6%
358 (Table 3). Little major morbidity was reported.

359
360 Concerning the robotic approach, 208 cases were reported in 15 teams, with 14
361 patients being excluded (Supplementary Table 3). If we except the multicentre study of
362 Salvo *et al.*[51], only one group published more than half of the cases. As cases from
363 Sweden and US are included in the very recent Salvo *et al.* study, recurrent rates were
364 evaluated taking account the said Salvo *et al.* study, and not the other teams included
365 in this Salvo *et al.* [51]; paper publishing also their cases previously in different
366 publications. It is not possible to calculate the recurrence rate according to disease
367 stage or tumor stage, because we do not have the initial characteristics of recurrent

368 patients (particularly between stage-IB1 or IB2 disease). Seventy-nine pregnancies
369 were observed in 55 patients. PR, LBR and PTR were respectively 77%, 74.6% and
370 23.5% (Table 3).

371 Comparing the recurrence rates according to the surgical approaches
372 (laparotomic *versus* mini-invasive surgery) in patients having stage-IB 1 & 2 diseases
373 (similarly to the inclusion criteria of the LACC trial), among 1,065 patients undergoing
374 a laparotomic RT, 35 recurrences (3.3%) were observed compared to 14 (5.5%)
375 among 254 having a mini-invasive approach (laparoscopic or robot-assisted)(NS). PR
376 and LBR in this last group are respectively 59.8% and 69.4% (Supplementary Figure
377 2).

378

379

380 **Recurrent rates in stage-IB1 and IB2 diseases (Figures 1 & 2)**

381

382 Figure 1 focuses on the recurrence rates observed according to 4 approaches:
383 simple cone/trachelectomy, VRT, RT by laparotomic and pure laparoscopic. We had
384 not evaluated the recurrence rate in stage-IB1 disease after NACT, because oncologic
385 rationale to expose patients to chemotherapy in a small tumor size is really
386 questionable. RT by robot-assisted laparoscopic approach was not included, because
387 of a lack of specific data in this subgroup of patients with smaller tumor sizes. PR and
388 LBR were added in this figure, but determined for the entire population of patients
389 undergoing these approaches. The lower rate of recurrence is observed in patients
390 undergoing the laparotomic approach (2.4% *versus* respectively 4.1%, 4.7%, and
391 5.2% for simple cone/trachelectomy, VRT and RT laparoscopic approach). On the
392 other hand, the lower PR is also observed in patients undergoing an open approach.

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

399

400 **Discussion**

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

413 omission of contributive information contained in smaller series [13]. In the current
414 review, we use the same methodology that we defined several years ago: a systematic
415 review integrating also case report(s) and very small series (having at least > 12
416 months of follow-up) and screening all authors/institution to avoid counting twice
417 duplicate series at different periods by the same institution. But our methodology (as
418 all the others used for similar systematic reviews) has also weaknesses such as
419 comparing series with different inclusion criteria, varied skilling of teams, sometimes
420 very few information about pathologic criteria (LVSI status, and depth of stromal
421 invasion, for exemple), lengths of follow-up, follow-up procedures used...
422 Nevertheless, the criteria that we defined to include papers seemed to us the most
423 suitable ones to compare the 5 strategies that are currently used to promote fertility in
424 early-stage cervical cancer, and also to allow opportune comparisons with what we
425 reported 6 years ago.

426 The results currently reported change drastically compared to what we
427 concluded previously. This is related to the number of cases reported combined with a
428 longer follow-up in older series. We globally doubled, or tripled in some strategies, the
429 number of cases analysed, increasing then from nearly 3,000 to 6,000 patients
430 selected for FSS (Table 3). Impacts are sometimes major: for example in simple
431 cone/trachelectomy, a single ambiguous recurrence was reported 6 years ago, *versus*
432 18 patients in the current analysis (Table 1). FSS, whatever the strategy used, should
433 be offered to young patients with conventional histotype (squamous carcinoma,
434 adenocarcinoma or adenosquamous lesion) and the most favourable prognostic
435 factors (no extracervical disease) treated by exclusive surgery. But how can we move
436 forward and define the best candidates for each procedure on the basis of accurate
437 and reproducible criteria?

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

454 For patients with the most favourable prognosis (stage-IB1 disease), the use of
455 a simple conisation/trachelectomy had been more widely reported in recent series
456 during the last 2 years. In 2016, we evaluated the recurrence risk < 0.5%, but since
457 then, and after reviewing the last reports, this rate is henceforth more accurately

458 evaluated to 4.1% (Table 3). Can we evaluate this rate in patients without LVSI? It is
459 not possible to calculate this rate in the current analysis, because very few series
460 reported their complete initial data of stage-IB1 disease (including LVSI status) and
461 recurrent disease. Nevertheless, we can observe that at least 6 of recurring stage-IB1
462 patients had no LVSI initially (Table 2). In the recent publication of the major CONCerv
463 trial, involving patients without LVSI, among 31 patients with stage-IB1 disease treated
464 with simple cone/trachelectomy, 1 (3%) recurred locally (data from K. Schmeler [33]).
465 This rate is then “robust”. It is not “0%”, and so this risk of recurrence of 1/30 should
466 then be exposed to patients before suggesting such a strategy. The ongoing GOG 278
467 trial (including patients treated with simple cone/trachelectomy and simple
468 hysterectomy) will probably improve information about the quality of life of such
469 management (NCT01649089). Anyway, the paper from Tomao *et al.* adds also
470 interesting data in this regard [24]. The risk of recurrence of the conisation/simple
471 trachelectomy (even if theoretically these procedures are “easy”) is decreased when
472 patients are treated in centers skilled to such strategy. This raises the following twofold
473 question: the length of free margins, particularly in stage-IB1 disease (with the
474 complex compromise between the length of free margins and the balance between the
475 size of the remaining uterus), and the quality of pathologic analysis of surgical
476 specimens. This paper is then a strong plea for the centralization of cases eligible for
477 FSS in “referent” centers really skilled to these strategies, even when a simple
478 cone/trachelectomy is planned [24]. Unfortunately we have no specific data about the
479 learning curve required for each procedure. In the open RT, particularly ligating the
480 uterine arteries, the technique is very comparable to the radical hysterectomy
481 procedure. But this learning curve effect is probably more important in mini-invasive,
482 vaginal approaches or with open RT with uterine arteries preservation, probably well
483 over 20 cases.

484 The VRT collects now nearly 2,000 cases. It requires really skilled surgeons to
485 the vaginal route (less thought in recent years). So, its use trends to decrease to the
486 benefit of abdominal approaches or simple cone/trachelectomy (Table 3).
487 Nevertheless, collecting additional cases, our analysis shows a consistent rate of
488 recurrence well indentified for 10 years (about 5%) and significant fertility results
489 (Supplementary Table 1). An increased rate of recurrence is observed in patients with
490 tumor size > 20 mm reaching then a nonacceptable rate of recurrence of 20.7% (Table
491 3). This is a clear limit to the safety of this procedure. But in the current analysis, unlike
492 what we reported 6 years ago, the LVSI status does impact significantly the recurrence
493 rate. Conventional patients with LVSI, being in the group of patients having
494 “intermediate risk factors”, are not eligible for FSS. But on the other hand, if we
495 summerized all papers published, nearly 1,000 patients undergoing FSS with LVSI
496 were reported (including anyway some cases of stage IA diseases)(Supplementary
497 Table 3). Indeed, the pathologic recognition of LVSI is sometimes complex. But a
498 recent and very interesting paper from the Roman group of Scambia *et al.* suggests
499 the use of a semi-quantitative evaluation of LVSI (negative *versus* focal *versus* diffuse)
500 to better evaluate the prognostic impact of this factor [69]. This is an interesting option,
501 because if FSS is clearly contra-indicated in patients with diffuse LVSI, similar to
502 lymphangitis (requiring then an adjuvant treatment), such a conservative strategy

503 could be probably considered in patients with stage-IB1 disease and focal LVSI
504 (having in the Ronsini *et al.* paper the same prognosis than patients without LVSI) [69].
505 If so, what should then be the best strategy in patients with focal LVSI: simple
506 cone/trachelectomy, a VRT or a RT by abdominal approach? The depth of stromal
507 invasion (< or > 10 mm and/or < or > 2/3 of the cervical stroma) should probably be
508 also integrated; still, we have no sufficient data to answer this question. Our analysis
509 suggests nevertheless that such a situation may be potentially the sole remaining
510 indication of the use of a vaginal approach to perform RT.

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

536 The last important results raised in the current paper pertain to the optimal
537 management of patients with tumor size > 20 mm. As we have very limited data of
538 such FSS in patients with tumor size > 40 mm and/or stage-IIA diseases (requiring a
539 higher rate of adjuvant treatment based on intermediate or high risk group), it is
540 impossible to evaluate its safety. We then continue to consider these situations as
541 contra-indication to the use of FSS. So, what is the best strategy for stage-IB2 disease
542 between 20 and 40 mm? The number of stage IB2 disease undergoing a laparoscopic
543 RT is very small (33 patients), it is then not possible to accurately evaluate the
544 oncological results of such approach in patients having a tumor size between 20 mm
545 and 40 mm. Even more, this rate could not be evaluated in patients treated using a
546 robotic approach, due to a lack of specific report for this subgroup of patients, whereas
547 the use of a robot-assisted laparoscopic approach to carry out a RT is increasing. The

548 2 most reported procedures in this context are NACT followed by conservative
549 approach and Open RT. Our current analysis demonstrated a risk of recurrence of
550 13.2% in patients undergoing NACT in stage-IB2 disease, drastically increased (the
551 double) compared to what we observed 6 years ago [5]. More cases added, more
552 recurrences reported, particularly during the last 3 years... Just to remind that the 4.5
553 year-DFS in patients treated radically with open surgery for tumor stage < 40 mm was
554 96.5% in the recent LACC trial... [1]. Nevertheless, these results should be taken with
555 caution, NACT is a very heterogeneous group in terms of combination of drugs used,
556 number of courses of neo-adjuvant chemotherapy, criteria to evaluate the response
557 before the surgery, criteria to define the radicality of the surgery...a very long list that
558 could be confusional factors. On the others hands our data are quite close to the
559 results of 2 recent review specifically dedicated to this topic [11,12]. Prospective trial or
560 obstervational studies could be very helpful to have a better view of the oncologic
561 results of such strategy, particularly in tumors > 20 mm. Two observational trials are
562 ongoing, one in China integrating stage-IB1 and IIA diseases (SYSUGO-
563 005/CSEM009 trial NCT02624531) and the NEOCON-F/CONTESSA trial dedicated
564 exclusively to stage-IB2 disease, involving 90 patients (NCT04016389)[71]. What
565 should be then the comparative group to evaluate the “safety or unsafety” of NACT?
566 What should be then the “non-acceptable” rate of recurrence to consider NACT for
567 stage-IB2 disease as unsafe, if so?

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

577

578 **Contributors**

579

580 **Designing the study:** PM, SG

581

582 **Extracting the data:** All authors

583

584 **Analysing the results:** PM, SG, AL, PP, CG, MG

585

586 **Approval of the manuscript:** All authors

587

588 **Conflict of interest**

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

590

591 **Funding**

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

595 **References**

- 596 1. Ramirez PT, Frumovitz M, Pareja R, Lopez A, Vieira M, Ribeiro R et al. Minimally
597 Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. *N Engl J Med.*
598 379 (2018) 1895-1904.
599
- 600 2. Cibula D, Pötter R, Planchamp F, Avall-Lundqvist E, Fischerova D, Haie Meder C
601 et al. The European Society of Gynaecological Oncology/European Society for
602 Radiotherapy and Oncology/European Society of Pathology Guidelines for the
603 Management of Patients With Cervical Cancer. *Int J Gynecol Cancer.* 28 (2018) 641-
604 655.
605
- 606 3. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri.
607 *Int J Gynaecol Obstet.* 143 Suppl 2 (2018) 22-36.
608
- 609 4. Dargent D, Martin X, Sacchetoni A, Mathevet P. Laparoscopic vaginal radical
610 trachelectomy: a treatment to preserve the fertility of cervical carcinoma patients.
611 *Cancer* 88 (2000) 1877-1882.
612
- 613 5. Bentivegna E, Gouy S, Maulard A, Chargari C, Leary A, Morice P. Oncological
614 outcomes after fertility-sparing surgery for cervical cancer: a systematic review. *Lancet*
615 *Oncol.* 17 (2016) e240-e253.
616
- 617 6. Bentivegna E, Maulard A, Pautier P, Chargari C, Gouy S, Morice P. Fertility
618 results and pregnancy outcomes after conservative treatment of cervical cancer: a
619 systematic review of the literature. *Fertil Steril.* 106 (2016) 1195-1211.
620
- 621 7. van Kol KGG, Vergeldt TFM, Bekkers RLM. Abdominal radical trachelectomy
622 versus chemotherapy followed by vaginal radical trachelectomy in stage 1B2 (FIGO
623 2018) cervical cancer. A systematic review on fertility and recurrence rates. *Gynecol*
624 *Oncol.* 155 (2019) 515-521.
625
- 626 8. Feng Y, Zhang Z, Lou T, Wang S, Bai H, Zhang Z. The security of radical
627 trachelectomy in the treatment of IA-IIA cervical carcinoma requires further evaluation:
628 updated meta-analysis and trial sequential analysis. *Arch Gynecol Obstet.* 299 (2019)
629 1525-1536.
630
- 631 9. Smith ES, Moon AS, O'Hanlon R, Leitao MM Jr, Sonoda Y, Abu-Rustum NR,
632 Mueller JJ. Radical Trachelectomy for the Treatment of Early-Stage Cervical Cancer:
633 A Systematic Review. *Obstet Gynecol* 13- (2020) 533-542.
634
- 635 10. Nezhat C, Roman RA, Rambhatla A, Nezhat F. Reproductive and oncologic
636 outcomes after fertility-sparing surgery for early stage cervical cancer: a systematic
637 review. *Fertil Steril.* 113 (2020) 685-703.
638
- 639 11. Gwacham NI, McKenzie ND, Fitzgerald ER, Ahmad S, Holloway RW.
640 Neoadjuvant chemotherapy followed by fertility sparing surgery in cervical cancers
641 size 2-4 cm; emerging data and future perspectives. *Gynecol Oncol.* 162 (2021) 809-
642 815.
643

- 644 12. Burbano J, Heredia F, Sanabria D, Ardila EG, Viveros-Carreño D, Rodriguez J.
645 Neoadjuvant chemotherapy prior to fertility-sparing surgery in cervical tumors larger
646 than 2 cm: a systematic review on fertility and oncologic outcomes. *Int J Gynecol*
647 *Cancer* 31 (2021) 387-398.
- 648
649 13. Kuznicki ML, Chambers LM, Morton M, Son J, Horowitz M, Crean-Tate KK,
650 Hackett L, Rose PG. Fertility-Sparing Surgery for Early-Stage Cervical Cancer: A
651 Systematic Review of the Literature. *J Minim Invasive Gynecol.* 28 (2021) 513-526.e1.
652
- 653 14. Maneo A, Sideri M, Scambia G, Boveri S, Dell'anna T, Villa M, Parma G, Fagotti
654 A, Fanfani F, Landoni F. Simple conization and lymphadenectomy for the conservative
655 treatment of stage IB1 cervical cancer. An Italian experience. *Gynecol Oncol.* 123
656 (2011) 557-560.
- 657
658 15. Raju SK, Papadopoulos AJ, Montalto SA, Coutts M, Culora G, Kodampur M,
659 Mehra G, Devaja O. Fertility-sparing surgery for early cervical cancer-approach to less
660 radical surgery. *Int J Gynecol Cancer* 22 (2012) 311-317.
- 661
662 16. Biliatis I, Kucukmetin A, Patel A, Ratnavelu N, Cross P, Chattopadhyay S, Galaal
663 K, Naik R. Small volume stage 1B1 cervical cancer: Is radical surgery still necessary?
664 *Gynecol Oncol.* 126 (2012) 73-77.
- 665
666 17. Al-Kalbani M, McVeigh G, Nagar H, McCluggage WG. Do FIGO stage IA and
667 small (≤ 2 cm) IB1 cervical adenocarcinomas have a good prognosis and warrant less
668 radical surgery? *Int J Gynecol Cancer* 22 (2012) 291-295.
- 669
670 18. Palaia I, Musella A, Bellati F, Marchetti C, Di Donato V, Perniola G, Benedetti
671 Panici P. Simple extrafascial trachelectomy and pelvic bilateral lymphadenectomy in
672 early stage cervical cancer. *Gynecol Oncol.* 126 (2012) 78-81.
- 673
674 19. Lindsay R, Burton K, Shanbhag S, Tolhurst J, Millan D, Siddiqui N. Fertility
675 conserving management of early cervical cancer: our experience of LLETZ and pelvic
676 lymph node dissection. *Int J Gynecol Cancer* 24 (2014) 118-123.
- 677
678 20. Bouchard-Fortier G, Reade CJ, Covens A. Non-radical surgery for small early-
679 stage cervical cancer. Is it time? *Gynecol Oncol.* 132 (2014) 624-627.
- 680
681 21. Choi MC, Jung SG, Park H, Lee SY, Lee C, Hwang YY, Kim SJ. Fertility
682 preservation by photodynamic therapy combined with conization in young patients with
683 early stage cervical cancer: a pilot study. *Photodiagnosis Photodyn Ther.* 11 (2014)
684 420-425.
- 685
686 22. Slama J, Cerny A, Dusek L, Fischerova D, Zikan M, Kocian R, Germanova A,
687 Cibula D. Results of less radical fertility-sparing procedures with omitted
688 parametrectomy for cervical cancer: 5years of experience. *Gynecol Oncol.* 142 (2016)
689 401-404.
- 690
691 23. Okugawa K, Kobayashi H, Sonoda K, Kaneki E, Kawano Y, Hidaka et al.
692 Oncologic and obstetric outcomes and complications during pregnancy after fertility-
693 sparing abdominal trachelectomy for cervical cancer: a retrospective review. *Int J Clin*
694 *Oncol.* 22 (2017) 340-346.
- 695

- 696 24. Tomao F, Maruccio M, Preti EP, Boveri S, Ricciardi E, Zanagnolo V, Landoni F.
697 Conization in Early Stage Cervical Cancer: Pattern of Recurrence in a 10-Year Single-
698 Institution Experience. *Int J Gynecol Cancer* 27 (2017) 1001-1008.
699
- 700 25. Demirkiran F, Kahramanoglu I, Bese T, Turan H, Meseci E, Arvas M. Simple
701 vaginal trachelectomy for early stage cervical cancer: A tertiary cancer center
702 experience. *Ginekol Pol.* 89 (2018) 475-480
703
- 704 26. Plante M, Renaud MC, Sebastianelli A, Gregoire J. Simple vaginal trachelectomy
705 in women with early-stage low-risk cervical cancer who wish to preserve fertility: the
706 new standard of care? *Int J Gynecol Cancer* 30 (2020) 981-986.
707
- 708 27. Li X, Xia L, Chen X, Fu Y, Wu X. Simple conization and pelvic lymphadenectomy
709 in early-stage cervical cancer: A retrospective analysis and review of the literature.
710 *Gynecol Oncol.* 158 (2020) 231-235.
711
- 712 28. Martinelli F, Ditto A, Filippi F, Vinti D, Bogani G, et al. Leone Roberti Maggiore U
713 et al. Conization and lymph node evaluation as a fertility-sparing treatment for early
714 stage cervical cancer. *Int J Gynecol Cancer* 31 (2021) 457-461.
715
- 716 29. Nica A, Marchocki Z, Gien LT, Kupets R, Vicus D, Covens A. Cervical conization
717 and lymph node assessment for early stage low-risk cervical cancer. *Int J Gynecol*
718 *Cancer* 31 (2021) 447-451.
719
- 720 30. Fanfani F, Pedone Anchora L, Di Martino G, Bizzarri N, Di Meo ML, Carbone V et
721 al. Oncologic and obstetric outcomes after simple conization for fertility-sparing
722 surgery in FIGO 2018 stage IB1 cervical cancer. *Int J Gynecol Cancer* 31 (2021) 452-
723 456.
724
- 725 31. Hruda M, Robova H, Rob L, Halaska MJ, Drozenova J, Pichlik T, Malikova H.
726 Twenty years of experience with less radical fertility-sparing surgery in early-stage
727 cervical cancer: Oncological outcomes. *Gynecol Oncol.* 2021 Jul 27:S0090-
728 8258(21)00593-X.
729
- 730 32. Breban-Kehl M, Zaccarini F, Sanson C, Maulard A, Scherier S, Genestie C et al.
731 Fertility preservation in cervical cancer, analysis of 30 years of practice and immersion
732 in future developments. *Gynecol Obstet Fertil Senol*; 2021:S2468-7189(21)00211-7.
733
- 734 33. Schmeler KM, Pareja R, Lopez Blanco A, Humberto Fregnani J, Lopes A,
735 Perrotta M et al. ConCerv: a prospective trial of conservative surgery for low-risk
736 early-stage cervical cancer. *Int J Gynecol Cancer* 2021:ijgc-2021-002921.
737
- 738 34. Plante M, Lau S, Brydon L, Swenerton K, LeBlanc R, Roy M. Neoadjuvant
739 chemotherapy followed by vaginal radical trachelectomy in bulky stage IB1 cervical
740 cancer: case report. *Gynecol Oncol.* 101 (2006) 367-370.
741
- 742 35. Landoni F, Preti E, Maneo A et al. Conservative surgery associated with
743 chemotherapy in early stage cervical cancer. *Gynecol Oncol.* 125 (2012) S58-S59.
744
745
746

- 747 36. Lanowska M, Mangler M, Speiser D et al. Radical vaginal trachelectomy after
748 laparoscopic staging and neoadjuvant chemotherapy in women with early-stage
749 cervical cancer over 2 cm: oncologic, fertility, and neonatal outcome in a series of 20
750 patients. *Int J Gynecol Cancer* 24 (2014) 586-593.
- 751 37. Salihi R, Leunen K, Van Limbergen E, Moerman P, Neven P, Vergote I.
752 Neoadjuvant chemotherapy followed by large cone resection as fertility-sparing
753 therapy in stage IB cervical cancer. *Gynecol Oncol.* 139 (2015) 447-451.
- 754 38. Estevez JP, Hequet D, Dubot C, Fourchette V, De La Motte Rouge T, Becette V,
755 Rouzier R. Fertility sparing treatment in women affected by cervical cancer larger than
756 2cm. *Bull Cancer* 103 (2016) 173-179.
- 757 39. Yan H, Liu Z, Fu X, Li Y, Che H, Mo R, Song L. Long-term outcomes of radical
758 vaginal trachelectomy and laparoscopic pelvic lymphadenectomy after neoadjuvant
759 chemotherapy for the IB1 cervical cancer: A series of 60 cases. *Int J Surg.* 29 (2016)
760 38-42.
- 761 40. Marchiolè P, Ferraioli D, Moran E, Mammoliti S, Tigaud JD, Beurrier F et al.
762 NACT and laparoscopic-assisted radical vaginal trachelectomy in young patients with
763 large (2-5 cm) high risk cervical cancers: Safety and obstetrical outcome. *Surg Oncol.*
764 27 (2018) 236-244.
- 765 41. Robova H, Rob L. Dose-dense neo-adjuvant chemotherapy followed by sentinel
766 node mapping and laparoscopic pelvic lymphadenectomy and simple trachelectomy in
767 cervical cancer. Updated results. ESGO 2019 meeting.
- 768 42. Lu Q, Zhang Z, Xiao M, Liu C, Zhang Z. The Surgical Morbidity And Oncological
769 Outcome Of Total Laparoscopic Radical Trachelectomy Versus Total Laparoscopic
770 Radical Hysterectomy For Early Stage Cervical Cancer: A Retrospective Study With
771 11-Year Follow-Up. *Onco Targets Ther.* 12 (2019) 7941-7947.
- 772 43. Wang A, Cui G, Jin C, Wang Y, Tian X. Multicenter research on tumor and
773 pregnancy outcomes in patients with early-stage cervical cancer after fertility-sparing
774 surgery. *J Int Med Res.* 47 (2019) 2881-2889.
- 775 44. Tesfai FM, Kroep JR, Gaarenstroom K, De Kroon C, Van Loenhout R, Smit V,
776 Trimbos B et al. Fertility-sparing surgery of cervical cancer >2 cm (International
777 Federation of Gynecology and Obstetrics 2009 stage IB1-IIA) after neoadjuvant
778 chemotherapy. *Int J Gynecol Cancer* 30 (2020) 115-121.
- 779 45. Okugawa K, Yahata H, Sonoda K, Ohgami T, Yasunaga M, Kaneki E, Kato K.
780 Safety evaluation of abdominal trachelectomy in patients with cervical tumors 2 cm: a
781 single-institution, retrospective analysis. *J Gynecol Oncol.* 31 (2020) e41.
- 782 46. Rendón GJ, Lopez Blanco A, Aragona A, Saadi JM, Di Guilmi J, Arab Eblen C,
783 Heredia Muñoz F, Pareja R. Oncological and obstetrical outcomes after neo-adjuvant
784 chemotherapy followed by fertility-sparing surgery in patients with cervical cancer 2
785 cm. *Int J Gynecol Cancer* 31 (2021) 462-467.
- 786 787 788 789 790 791 792 793 794 795 796

- 797 47. de Vincenzo R, Ricci C, Fanfani F, Gui B, Gallotta V, Fagotti A, Ferrandina G,
798 Scambia G. Neoadjuvant chemotherapy followed by conization in stage IB2-IIA1
799 cervical cancer larger than 2 cm: a pilot study. *Fertil Steril*. 115 (2021) 148-156.
800
- 801 48. Aarts JWM, Zusterzeel PLM. Neoadjuvant Chemotherapy Followed by Vaginal
802 Radical Trachelectomy as Fertility-Preserving Treatment for Patients with FIGO 2018
803 Stage 1B2 Cervical Cancer. *Arch Obstet Gynecol*. 2 (2021) 16-19.
804
- 805 49. Sanson C, Zaccarini F, Maulard A, Scherrier S, Pautier P, Leary A, Gouy S,
806 Morice P. Neoadjuvant chemotherapy in fertility sparing management of stage IB2
807 cervical cancer: a real-life short series. In press
808
- 809 50. Machida H, Iwata T, Okugawa K, Matsuo K, Saito T, Tanaka K, Morishige K et al.
810 Fertility-sparing trachelectomy for early-stage cervical cancer: A proposal of an ideal
811 candidate. *Gynecol Oncol*. 156 (2020) 341-348.
812
- 813 51. Salvo G, Ramirez PT, Leitao MM, Cibula D, Wu X, Falconer H et al. Open Versus
814 Minimally Invasive Radical Trachelectomy in Early-Stage Cervical Cancer:
815 International Radical Trachelectomy Assessment Study. *Am J Obstet Gynecol*.
816 2021:S0002-9378(21)00963-7.
817
- 818 52. Pomel C, Castaigne D, Atallah D et al. Laparoscopic (type III Piver like) radical
819 trachelectomy. *EJSO*. 28 (2002) 302.
820
- 821 53. Park NY, Chong GO, Cho YL, Park IS, Lee YS. Total laparoscopic nerve-sparing
822 radical trachelectomy. *J Laparoendosc Adv Surg Tech A*. 19 (2009) 53-58.
823
- 824 54. Martin A, Torrent A. Laparoscopic nerve-sparing radical trachelectomy: surgical
825 technique and outcome. *J Minim Invasive Gynecol*. 17 (2010) 37-41.
826
- 827 55. Park JY, Joo WD, Chang SJ, Kim DY, Kim JH, Kim YM, Kim YT, Nam JH. Long-
828 term outcomes after fertility-sparing laparoscopic radical trachelectomy in young
829 women with early-stage cervical cancer: an Asian Gynecologic Cancer Group (AGCG)
830 study. *J Surg Oncol*. 110 (2014) 252-257.
831
- 832 56. Hong DG, Lee YS, Park NY, Chong GO, Park IS, Cho YL. Robotic uterine artery
833 preservation and nerve-sparing radical trachelectomy with bilateral pelvic
834 lymphadenectomy in early-stage cervical cancer. *Int J Gynecol Cancer* 21 (2011) 391-
835 396.
836
- 837 57. Ebisawa K, Takano M, Fukuda M, Fujiwara K, Hada T, Ota Y, Kurotsuchi S,
838 Kanao H, Andou M. Obstetric outcomes of patients undergoing total laparoscopic
839 radical trachelectomy for early stage cervical cancer. *Gynecol Oncol*. 131 (2013) 83-
840 86.
841
- 842 58. Kucukmetin A, Biliatis I, Ratnavelu N, Patel A, Cameron I, Ralte A, Naik R.
843 Laparoscopic radical trachelectomy is an alternative to laparotomy with improved
844 perioperative outcomes in patients with early-stage cervical cancer. *Int J Gynecol*
845 *Cancer* 24 (2014) 135-140.
846

- 847 59. Yoon A, Choi CH, Lee YY, Kim TJ, Lee JW, Kim BG, Bae DS. Perioperative
848 Outcomes of Radical Trachelectomy in Early-Stage Cervical Cancer: Vaginal Versus
849 Laparoscopic Approaches. *Int J Gynecol Cancer* 25 (2015) 1051-1057.
850
- 851 60. Vieira MA, Rendón GJ, Munsell M et al. Radical trachelectomy in early-stage
852 cervical cancer: A comparison of laparotomy and minimally invasive surgery. *Gynecol*
853 *Oncol.* 138 (2015) 585-589.
854
- 855 61. Yoo SE, So KA, Kim SA, Kim MK, Lee YK, Lee IH, Kim TJ, Lee KH. Surgical and
856 obstetrical outcomes after laparoscopic radical trachelectomy and pelvic
857 lymphadenectomy for early cervical cancer. *Obstet Gynecol Sci.* 59 (2016) 373-378.
858
- 859 62. Saadi JM, Perrotta M, Orti R, Salvo G, Giavedoni ME, Gogorza S, Testa R.
860 Laparoscopic radical trachelectomy: technique, feasibility, and outcomes. *JSLs.* 19
861 (2015) e2013.00248.
862
- 863 63. Balaya V, Lécuru F, Magaud L, Ngô C, Huchon C, Bats AS, Mathevet P.
864 Perioperative morbidity of radical trachelectomy with lymphadenectomy in early-stage
865 cervical cancer: a French prospective multicentric cohort. *J Gynecol Oncol.* 30 (2019)
866 e34.
867
- 868 64. Lu Q, Liu C, Zhang Z. Total laparoscopic radical trachelectomy in the treatment
869 of early-stage cervical cancer: review of technique and outcomes. *Curr Opin Obstet*
870 *Gynecol.* 26 (2014) 302-307.
871
- 872 65. Chernyshova A, Kolomiets L, Chekalkin T, Chernov V, Sinilkin I, Gunther V et al.
873 Fertility-Sparing Surgery Using Knitted TiNi Mesh Implants and Sentinel Lymph
874 Nodes: A 10-Year Experience. *J Invest Surg.* 2020:1-9.
875
- 876 66. Iwata T, Machida H, Matsuo K, Okugawa K, Saito T, Tanaka K, Morishige K,
877 Kobayashi H, Yoshino K, Tokunaga H, Ikeda T, Shozu M, Yaegashi N, Enomoto T,
878 Mikami M. The validity of the subsequent pregnancy index score for fertility-sparing
879 trachelectomy in early-stage cervical cancer. *Fertil Steril.* 115 (2021) 1250-1258.
880
- 881 67. Kanao H, Aoki Y, Fusegi A, Omi M, Nomura H, Tanigawa T et al. Feasibility and
882 Outcomes of "No-Look No-Touch" Laparoscopic Radical Trachelectomy for Early-
883 Stage Cervical Cancer. *J Clin Med.* 10 (2021) 4154.
884
- 885 68. Uzan C, Gouy S, Desroque D, et al. Analysis of a continuous series of 34 young
886 patients with early-stage cervical cancer selected for a vaginal radical trachelectomy:
887 should "staging" conization be systematically performed before this procedure? *Int J*
888 *Gynecol Cancer* 23 (2013) 331-336.
889
- 890 69. Ronsini C, Anchora LP, Restaino S, Fedele C, Arciuolo D, Teodorico E et al. The
891 role of semiquantitative evaluation of lympho-vascular space invasion in early stage
892 cervical cancer patients. *Gynecol Oncol.* 162 (2021) 299-307.
893
- 894 70. Chao X, Li L, Wu M, Wu H, Ma S, Tan X, Zhong S, Lang J. Minimally invasive
895 versus open radical trachelectomy for early-stage cervical cancer: protocol for a
896 multicenter randomized controlled trial in China. *Trials* 21 (2020) 1022.
897
898

899 71. Plante M, van Trommel N, Lheureux S, Oza AM, Wang L, Sikorska K et al. FIGO
900 2018 stage IB2 (2-4 cm) Cervical cancer treated with Neo-adjuvant chemotherapy
901 followed by fertility Sparing Surgery (CONTESSA); Neo-Adjuvant Chemotherapy and
902 Conservative Surgery in Cervical Cancer to Preserve Fertility (NEOCON-F). A PMHC,
903 DGOG, GCIG/CCRN and multicenter study. *Int J Gynecol Cancer* 29 (2019) 969-975.

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 x 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 ASC***	4 (range, 1-4)***	15 Positive***	PLND	LEEP/Conisation /reconisation	17 pts attempting. 4 pts pregn.	No recurrence 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*****

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 classification

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

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, Paclitaxel, 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	Currently 14-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 Maneo 2008 ³⁵	21/16**	IB2 < 30 mm (8 ≥ 20 mm)	9 SCC 12 ADC	9 Cisplatin, Paclitaxel, Ifosfamide 12 Cisplatin, Paclitaxel, Epirubicin	3	PLND + CKC	8 No invasive RD 9 RD < 3 mm 4 RD > 3 mm	9 pts attempting 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		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	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) Mean FU 23 months
Lanowska 2014* ³⁶		1 IIA1	1 ASC				4 RD > 5 mm	2 Premature deliveries	NED 6, 23 & 63 mths
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 4 pts attempting	
Choi 2014 ²¹	5	4 IB 2, 1 IIA1 7 IB1	5 SCC	Cisplatin + Etoposide or Paclitaxel	3	PLND + Conisation + Photodynamic therapy	1 had RD > 2 cm	2 pregnancies in 2 pts At term delivery	No recurrence FU 60 mths
Salihi 2015 ³⁷	11/9**	3 IB2 4 ADC 1 IB3	6 SCC 4 ADC 1 ASC	2 Cisplatin, Paclitaxel, Ifosfamide 9 Carboplatin, Paclitaxel	3****	7 CKC**** 3 Laser conisation	8 No RD 2 RD (1 with involved margins) 1 Progressive disease not undergoing conisation	9 pts attempting 11 pregnancies in 6 pts 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, Paclitaxel	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 1 st or 2 nd trimester misc.	1 recurrence FU 43 mths
Poka 2017	1	1 IB2 30 mm 10 IB2	NEC	NR	NR	PLND + ART	NR	No	Recurrence at 3 mths DOD
Marchiole 2011, 2018 ⁴⁰	19	5 IB3 4 IIA1	11 SCC 8 ADC	Cisplatin, Paclitaxel, Ifosfamide Cisplatin, Paclitaxel, Epirubicin	3 or 4	PLND + VRT	7 no RD 5 < 3 mm 5 > 3 mm	5 pts attempting 8 pregnancies in 3 patients 3 live birth 4 T1 foetal loss 1 interruption	2 recurrences (local) IB2 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 1 st 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, Paclitaxel, 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 local & 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

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

IVF: In Vitro Fertilization; IUI: Intra-uterine Insemination. FU: Follow-up. DOD: Died of Disease; T1: 1st Trimester of the pregnancy.

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 2-4 cm***	0	101	375	33	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 1 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
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 pterm 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****	No recurrence FU 80 mths
Chernyshova 2020 ⁶⁵	39	No specific report	No specific report	NR	NR	Yes	No	NR	No cervical stenosis	9 pregnancies (7 spontaneous) 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

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.

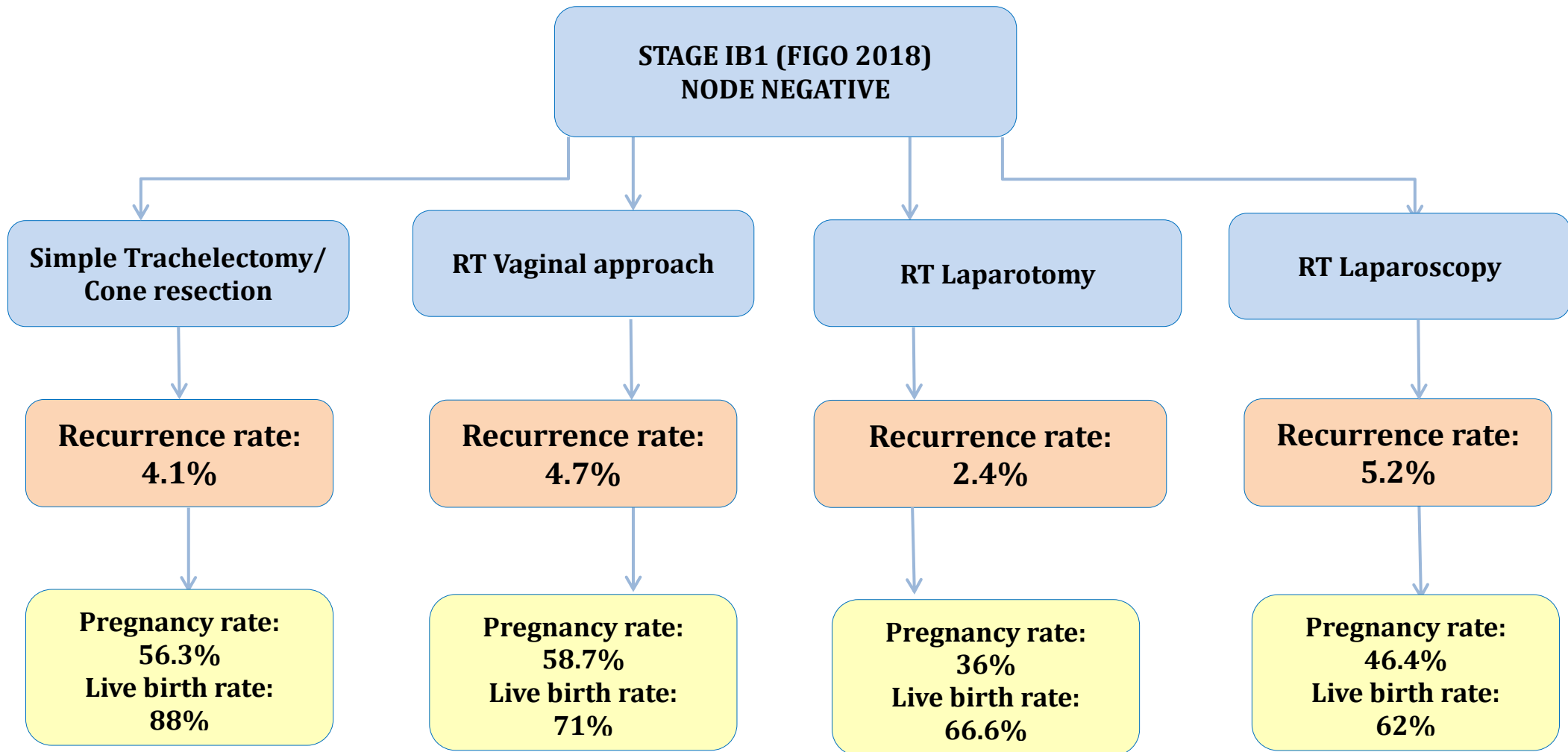
****: 13 pts receiving neoadjuvant chemotherapy; fertility results being reported in the series published in 2014.

*****: laparoscopic trachelectomy including laparoscopic-assisted surgery.

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.

Figure 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.

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

