Open access • Journal Article • DOI:10.1136/IJGC-2019-000398

FIGO 2018 stage IB2 (2-4 cm) Cervical cancer treated with Neo-adjuvant chemotherapy followed by fertility Sparing Surgery (CONTESSA); Neo-Adjuvant Chemotherapy and Conservative Surgery in Cervical Cancer to Preserve Fertility (NEOCON-F). A PMHC, DGOG, GCIG/CCRN and multicenter study. — Source link

Marie Plante, Nienke E. van Trommel, Stephanie Lheureux, Amit M. Oza ...+6 more authors

Institutions: Netherlands Cancer Institute, University of Amsterdam

Published on: 01 Jun 2019 - International Journal of Gynecological Cancer (Int J Gynecol Cancer)

Topics: Adjuvant therapy and Cervical cancer

FIGO 2018 Stage IB2 (2-4 cm) Cervical cancer treated with Neoadjuvant chemotherapy followed by fertility Sparing Surgery (CONTESSA)

Neo-Adjuvant Chemotherapy and Conservative Surgery in Cervical Cancer to Preserve Fertility (NEOCON-F)

Marie Plante MD[1], Nienke van Trommel MD PhD[2], Stephanie Lheureux MD[3], Amit Oza MD[3], Lisa Wang MSc[3], Karolina Sikorska PhD[4], Sarah E Ferguson MD[5], Katy Han MD MSc[6], Frédéric Amant MD PhD[2,7]

AFFILIATION:

[1] Centre Hospitalier Universitaire de Québec

L'Hôtel-Dieu de Québec

Division of Gynecologic Oncology

Laval University, Quebec City, Canada

[2] Netherlands Cancer Institute

Center for Gynecologic Oncology Amsterdam

Netherlands Cancer Institute

Amsterdam, The Netherlands

[3]Princess Margaret Consortium

Drug Development Program

Toronto, ON, Canada

[4] Netherlands Cancer Institute

Department of Biostatistics

Amsterdam, The Netherlands

[5] Princess Margaret Cancer Centre

Department of Obstetrics and Gynecology

Division of Gynecologic Oncology

University of Toronto

Toronto, ON, Canada

[6] Princess Margaret Cancer Centre
Radiation Medicine Program
Department of Radiation Oncology
University of Toronto
Toronto, ON, Canada

[7] Amsterdam University Medical Centers
Center for Gynecologic Oncology
Amsterdam, The Netherlands

MAILING ADDRESS for CORRESPONDENCE:

Dr. Marie Plante
Professor
L'Hôtel-Dieu de Québec
Gynecologic Oncology Division
11 Côte du Palais, Quebec City, CANADA
G1R-2J6
TEL: 418-691-5392
FAX: 418-691-5720
E-mail: marie.plante@crhdq.ulaval.ca

Disclaimers. The views expressed in this manuscript are my own and that of my co-authors and not an official position of the institution or funder

Source of support.
The Princess Margaret Consortium is responsible for the funding of Canadian sites' accrual and for the overall data management
Each Cooperative Group is responsible for its own funding

Word count: **2940**. Authorization to exceed the word count by a maximum of 500 has been obtained from Editor in chief

Number of figures and tables: 1 Figure and 4 Tables

Conflict of Interest declaration. Authors declare no conflict of interest

1) Introduction

Almost 40% of women with cervical cancer are diagnosed between the age of 20 and 44 with disease confined to the cervix in approximately 46%.[1] The radical trachelectomy procedure is now recognized as an alternative to the "standard" radical hysterectomy for young women with lesions <2 cm who wish to preserve fertility as per NCCN guidelines.[2] It is reassuring that a recent SEER data analysis shows that uterine preserving surgery (UPS) such as cone/trachelectomy is not associated with a higher risk of death compared to non-UPS (hysterectomy). [3] However, in that analysis, risk factors independently associated with worsened outcome included lesion size >2cm, adenosquamous histology, and lymph node positivity. Other series and literature reviews have also shown that size of the lesion is one of the most important prognostic factors in terms of outcome, with a statistically increased risk of recurrence for patients with lesions >2 cm. [4-6]

Upfront radical trachelectomy

Currently, standard treatment for larger cervical cancer measuring 2-4 cm is a definitive radical **hysterectomy** which is associated with recurrence rates of 13% and a 5-year recurrence free survival of 87%.[7] Obviously, this option precludes fertility preservation. To date, the optimal management of women with lesions >2 cm who wish to preserve fertility is not well defined. One option is the upfront abdominal radical trachelectomy (ART) procedure. The rates of fertility preservation vary significantly amongst different series as is the rate of lymph node positivity and adjuvant treatments (10-45%).[6,8-10] Even though the procedure is "technically" feasible and allows more radical parametrial resection, a high proportion of patients require adjuvant radiotherapy based on high-risk features (positive nodes, margins or parametrium) or intermediate-risk factors (tumor size, depth of stromal invasion and lympho-vascular invasion (LVSI)) identified on final pathology.[11] Adjuvant radiotherapy not only precludes the chances of childbearing but it also ruins ovarian function, leading to definitive premature menopause and permanent impact on quality of life (QoL) and sexual health. For patients who end up preserving their fertility potential following ART, the fertility rate and obstetrical outcome appear to be reduced.[6] A recent series of 151 ART confirms that infertility treatments were frequently required following ART and that premature rupture of membranes and premature labor were frequently observed.[12] The same group recently reported a high complication rate post ART resulting in infertility in up to 73% of cases.[13]

Neo-adjuvant chemotherapy (NACT) followed by fertility-sparing surgery (FSS)

There is available data on the use of NACT followed by radical hysterectomy showing that it is effective in reducing the size of cervical cancer lesions.[14] A Cochrane meta-analysis of 1078 patients including bulky stage 1B (the population of interest for this trial), IIB and IIIB disease showed that NACT followed by surgery improves OS and PFS compared to surgery alone and is associated with a 23% reduction in risk of death.[15] Other retrospective reviews and meta analyses including data from observational studies have confirmed that NACT for stage 1A2-1B disease reduces the need for adjuvant radiotherapy, and is associated with decreased tumour size, lymph node involvement and distant metastases.[16] Globally the reported response rate to NACT is in the range of 70%. Conversely, suboptimal response to NACT appears to be an independent prognostic factor of poorer outcome. [17]

Considering the above, the concept of NACT was applied to young women who wish to preserve fertility in order to reduce the lesion size and subsequently allow FSS. Review of five studies of

NACT followed by FSS showed a 71% response rate and better obstetrical outcome compared to upfront trachelectomy.[18] However, patients with suboptimal chemotherapy response are at higher risk of recurrence and death suggesting that the lack of response to NACT is a marker of worse outcome.[16,19] Bentivegna *et al.* reviewed data from 17 series and case reports of NACT followed by less radical surgery confirming good oncologic outcome in good chemo-responders.[6] In addition, obstetrical outcome is favorable following that approach and appears superior compared to patients undergoing upfront radical trachelectomy.[6,17] A very recent meta-analysis and meta-regression totalizing 86 patients who underwent NACT followed by FSS confirms that more radical surgery results in less favorable pregnancy outcome compared to less radical surgery.[20]

Unsettled issues

- **Lymph node staging**

Even though NACT can potentially convert node positive to node negative patients[14,17,21] and could allow the option of fertility preservation to these patients, we felt that positive node is a marker of more advanced disease and not appropriate for FSS. Indeed, Vercellino *et al.* reported a much higher recurrence rate in node positive patients.[22] The recent SEER data analysis also clearly identifies node positivity as an independent prognostic factor of poorer outcome.[3] This is why, as part of eligibility criteria for this trial, patients have to first undergo lymph node evaluation and be pathologically node negative.

Sentinel node mapping (SLN) has been extensively performed as part of the surgical staging of cervical cancer and shows high sensitivity (96.4%) and negative predictive value (99.3%). [23] Indocyanine Green (ICG) is becoming the most widely used tracer for SLN mapping with excellent bilateral detection rate (91.7%) in patients with stage IB1 > 2cm, the group of interest in this study. [24] A prospective randomized trial (FILM study) also confirmed the superiority of ICG over blue dye for SLN mapping. [25] However, as pointed out recently by Cibula et al., there are currently no prospective evidence demonstrating the **long-term oncologic safety** of SLN alone in cervical cancer. [26] Data from two large ongoing prospective trials are awaited (SENTIX = NCT02494063; SENTICOL III= NCT03386734). Therefore, as part of this study, to ensure safety and quality control, patients are required to undergo complete pelvic lymph node dissection in addition to SLN mapping.

- **Chemotherapy agents**

Italian studies have shown that the combination of Paclitaxel, Ifosfamide and Cisplatin compared to Paclitaxel and Cisplatin is more effective in locally advanced cervical cancer but clearly more toxic.[27] In addition, given that Ifosfamide (alkylating agent) may potentially be gonadotoxic, most investigators have dropped the Ifosfamide from the combination. Lorusso *et al*. have conducted a systematic literature review and concluded that carboplatin represents a valid and less toxic alternative compared to cisplatin.[28] A Japanese large randomized trial also shows that 3-weekly Paclitaxel/Carboplatin is not inferior to Paclitaxel/Cisplatin but less toxic.[29] More recently, weekly dose-dense Paclitaxel 80mg/m^2 with Carboplatin AUC2 regimen has been studied in locally advanced cervical cancer with an objective response rate ranging between 68-87%.[30] Interestingly, Sahili *et al.* reported their experience with a slightly modified regimen (weekly Paclitaxel 60mg/m^2 with Carboplatin AUC 2.7) with good response rate but with limited alopecia, a potentially important consideration for young women in terms of QoL.[31] Therefore, as part of this study, the

chemotherapy regimen will be based on platinum-paclitaxel therapy but sequence and platinum choice is left at the investigator's discretion.

- **Type of Fertility Sparing Surgery**

There is clearly a trend towards less radical surgery in patients with lesions < 2cm, since the probability of parametrial extension in those cases is very low.[32] The SHAPE trial is currently ongoing and prospectively compares radical hysterectomy vs simple hysterectomy in these low risk patients.[33] In addition, a recent SEER data analysis comparing modified radical surgery versus less radical surgery for stage IB1 lesions showed no difference in 10-year disease free survival, which is reassuring.[34] There is a similar trend towards less radical surgery in women who wish to preserve fertility. Several series, reviews and meta-analysis have shown excellent oncologic and improved obstetrical outcome following simple trachelectomy or cone versus radical trachelectomy.[3,6,35,36] Therefore, simple trachelectomy or large cone would appear to be adequate surgery in patients with complete/partial response (residual tumor < 2cm) following NACT.

In summary, most of the available data on NACT followed by FSS come from limited small retrospective studies using a variety of treatment approaches. Thus, there is a lack of standardized approach with regards to the optimal management of these patients. Hence, we have developed this proposal with the hopes of providing solid, prospective meaningful data with regards to the safety of this treatment approach, its potential to preserve fertility, and ultimately the possibility for these young women to successfully become pregnant.

2) Methods

a) Trial Design

This is a multi-center, prospective single arm phase II trial addressing the safety of NACT followed by FSS in young women with FIGO 2018 stage IB2 cervical cancer[37] with lesions measuring 2-4 cm and who wish to preserve fertility.

Patients have to be under the age of 40 and be premenopausal. Lesion size has to be assessed by pelvic MRI and physical examination. Squamous, adenocarcinoma and adenosquamous histology, all grades, and LVSI are allowed. Pre-study entry criteria include a pelvic lymph node dissection +/- SLN mapping to exclude node positive patients.

Eligible patients will undergo three cycles of platinum based chemotherapy in combination with paclitaxel. The choice of the chemotherapy regimen and schedule will be left at the discretion of the treating physicians. It is anticipated that most patients will receive a combination of Paclitaxel 175mg/m^2 with Carboplatin AUC6 every 3 weeks or a weekly Paclitaxel 80mg/m^2 and Carboplatin AUC2 regimen. The use of cisplatin instead of carboplatin is allowed (Paclitaxel 135mg/m^2 and Cisplatin 50mg/m^2 every 3weeks).

Following three cycles of NACT, a clinical examination and pelvic MRI will be performed to assess tumor response. Patients with complete or partial response (lesion < 2cm) will then proceed to FSS. The type of FSS procedure will be left at the discretion of the treating physicians (simple trachelectomy/large cone). It is anticipated that approximately 10% of patients may require adjuvant radiotherapy following FSS based on risk factors identified on final pathological

evaluation of the cervical specimen (margin status, LVSI, depth of stromal invasion). Adjuvant treatment will be recorded and left at the investigators' discretion. Patients with positive/close surgical margins may be allowed to undergo additional surgery (local re-excision or definitive hysterectomy). Patients will be monitored for two and three years for disease recurrence. Information on obstetrical outcome in patients who become pregnant during the follow-up period (3 years) will be collected.

This trial is co-led by the Princess Margaret Hospital Consortium (PMHC) and the Dutch Gynecologic Oncology Group. Different sites across Canada and the Netherlands will open the trial given the selected population. The trial will also be available to other cooperative groups/sites under the GCIG/CCRN (Cervical Cancer Research Network) umbrella.

b) Participants and Outcomes

Inclusion and exclusion criteria are listed in Table 1. Primary and secondary objectives and endpoints are listed in Table 2 and Table 3, and exploratory objectives are listed in Table 4.

c) Sample Size – Statistical Methods

If at most 45% of patients are able to retain functional uterus after the NACT, the treatment would be considered clinically not sufficiently interesting. We expect a success rate of at least 60%. Setting a one-sided alpha level to 0.025 and power to 80%, **90 women** are required to test H0: $P \leq 45\%$ versus H1: $P > 60\%$ using a one group $\chi 2$ test**.**

Prior distribution of recurrence rate at 2 years is assumed to be beta which corresponds to mean of 10% and standard deviation of 6.5%. The monitoring will start after 5 patients are accrued and followed until recurrence for at least 2 years. The trial will be considered unsafe if there is at least 70% probability that 2-year recurrence rate is above 10%. The stopping boundaries are calculated using Jack Lee's Bayesian Efficacy/Safety Monitoring Via Posterior Probability (https://biostatistics.mdanderson.org/softwareOnline/) .

In case if the stopping criteria is met for a subset of accrued patients who already have sufficient follow-up, but there are more accrued patients in the trial (*who do not have sufficient follow-up data*), the accrual will be put on hold until all patients accrued reach 2 year follow-up (*followed for 2 years*). If the stopping criteria is still met after the updated data is obtained, only then the trial will stop early.

The trial will be monitored by a DSMB who will meet every 6 months to review all the data on the trial.

d) Quality of Life (QoL) studies:

One of the objectives of this study is to evaluate the patient reported outcomes (PROSs) including QoL, sexual health, anxiety/depression and reproductive concerns in women undergoing FSS after NACT. Patients will complete PROs measures at baseline (before starting NACT), before FSS, and postoperatively (6 weeks and at 3, 6, 12, 24 and 36 months). Questionnaires will be completed through email (with a secure link) or paper questionnaire (with a pre-paid self-addressed

envelope). The PROSs will be assessed using the following validated questionnaires: the Functional Assessment after Cancer Therapy- Cervix (FACT-cx), the Reproductive Concerns after Cancer (RCAC), the Female Sexual Functioning Index (FSFI), the Sexual Adjustment and Body Image Scale (SABIS-G) and the illness intrusiveness scale.

e) Correlative Studies: Disease monitoring

- By Human Papillomavirus Virus (HPV) circulating DNA (ctDNA/cfDNA)

Tumors release DNA into the circulation, where they can be measured noninvasively to assess disease burden. The majority of cervical cancers are caused by HPV; HPV DNA can provide a unique marker that distinguishes tumor-derived DNA from normal, non-malignant sources of cell-free DNA. Digital polymerase chain reactive (dPCR) is an ultrasensitive and affordable technique for absolute quantification of DNA. For patients with locally advanced cervical cancer, we recently showed using dPCR 100% sensitivity for detecting plasma HPV DNA at baseline, and that detectable plasma HPV DNA at the end of chemoradiation is associated with inferior progression-free survival. [38] We hypothesize that detectable plasma HPV DNA at the end of NACT and after FSS will be associated with inferior PFS. Peripheral blood will be collected at different time-points during treatment and plasma will be isolated for the measurement of HPV DNA by dPCR: baseline, chemotherapy cycle 2, surgery, and 3-month follow-up visit.

- By hypermethylated DNA (hmDNA) measurements in cervical scrapes

Molecular host cell alterations which are associated with and contribute to cervical carcinogenesis can be potentially useful as biomarkers for the prediction of response to NACT and might serve as a reliable test in follow-up. Among these host cell alterations, DNA methylation is a well-studied epigenetic event during cervical carcinogenesis. [39] DNA methylation markers have been shown to be valuable in the post-treatment monitoring of CIN2/3 lesions to identify women with an increased risk of recurrence.[40] Currently, we are testing the value of DNA methylation markers in the follow-up of untreated CIN lesions (CONCERVE study, NTR6069). Methylation markers have also shown to be promising in the response prediction of chemoradiation in cervical cancer patients.[41] We hypothesize that these markers can serve as predictors for response to NACT and that recurrence of disease will be detected early by measuring these markers in cervical scrapes. Cervical scrapes will be collected prior to the start of chemotherapy, before FSS and during every follow-up visit for three years by ThinPrep^{C}. Targeted detection of multiple methylated genes will be performed by multiplex quantitative methylation-specific PCR (qMSP).

3. Discussion

This phase II trial offers a well-standardized approach to the management of a very selected group of patients: young women with larger cervical cancer lesions (2-4 cm) who wish to preserve fertility. This trial will provide prospective solid data to evaluate the safety of the proposed trial and the probability of ultimately retaining fertility potential (functional uterus). Considering that these cases are relatively rare, and that individual investigators/centers encounter few of those cases per year, international collaboration will be key to the success of this trial, which is why it is conducted under the GCIG/CCRN leadership.

We expect that the majority of patients will successfully complete 3 cycles of the NACT,

considering that the toxicity of the proposed chemotherapy regimen in this young and generally healthy patient population should not be a major issue. Following completion of NACT, we expect that approximately 70% of patients will have a complete or partial response (residual tumor <2 cm) based on clinical evaluation and pelvic MRI. These patients will then proceed with FSS and be monitored for 2 and 3 years. Information on potential adjuvant therapy post FSS will be collected as well as data on obstetrical outcome of patients who have become pregnant during the follow-up period (3 years).

We expect that the majority of patients (85-90%) will not require adjuvant treatment following FSS. However, in the event of risk factors identified on final pathology evaluation of the cervical specimen (positive/close margins, LVSI or deep stromal invasion), adjuvant treatment may be required according to local practice (either definitive radical hysterectomy or definitive chemoradiation). Re-excision procedure might be possible in selected patients with positive/close surgical margins. In addition, in the event of suboptimal chemotherapy response (residual tumor ≥ 2cm), stable disease or disease progression, FSS will be abandoned and definitive radical hysterectomy or chemoradiation will be recommended according to local practice. Data on the requirement of tri-modality therapy and data on patients with suboptimal response/progression on NACT will be collected and may ultimately serve to help improve patients' selection.

This trial will also provide important QoL information regarding the tolerability and "acceptability" of chemotherapy in this young patient population as well as its impact on ovarian function. Lastly, this trial will provide a unique opportunity to conduct translational research by monitoring tumor response either by serial measurements of serum ctDNA or hypermethylated DNA (hmDNA) measurements in cervical scrapes.

In summary, we believe that this trial has the potential to influence current practice by providing clinicians a standardized treatment approach to treat young women with larger cervical cancer lesions (2-4 cm) who wish to preserve fertility. We designed a feasible, flexible and simple protocol that will allow patients enrollment in different countries. Based on the parameters provided in this trial, we believe that the proposed treatment schema is safe and provides these young women the option of preserving their ovarian and reproductive function.

Acknowledgement:
Smitha Udagani for her help and support in the preparation and review of the protocol and manuscript.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics 2018. CA Cancer J Clin. 2018;68:7-30.

2. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Cervical Cancer. Version 1.2017.

3. Tseng JH, Aloisi A, Sonoda Y, Gardner GJ, Zivanovic O, Abu-Rustum NR, Leitao MM Jr. Long-Term Oncologic Outcomes of Uterine-Preserving Surgery in Young Women With Stage Ib1 Cervical Cancer. Int J Gynecol Cancer 2018; 150(1):44-49.

4. Plante M, Gregoire J, Renaud MC, Roy M. The vaginal radical trachelectomy: an update of a series of 125 cases and 106 pregnancies. Gynecol Oncol 2011; 121:290.

5. Hauerberg L, Høgdall C, Loft A, Ottosen C, Bjoern SF, Mosgaard BJ, Nedergaard L, Lajer H. Vaginal Radical Trachelectomy for early stage cervical cancer. Results of the Danish National Single Center Strategy. Gynecologic Oncology 2015;138 :304–310.

6. Bentivegna E, Gouy S, Maulard A, et al. Oncological outcomes after fertility-sparing surgery for cervical cancer: a systematic review. Lancet Oncol 2016; 17(6):e240-253.

7. Park JY, Kim DY, Kim JH, Kim YM, Kim YT, Nam JH. Outcomes after radical hysterectomy according to tumor size divided by 2-cm interval in patients with early cervical cancer. Ann Oncol 2011;22(1):59-67.

8. Wethington SL1, Sonoda Y, Park KJ, et al. Expanding the indications for radical trachelectomy: a report on 29 patients with stage IB1 tumors measuring 2 to 4 centimeters. Int J Gynecol Cancer 2013;23:1092-1098.

9. Li J, Wu X, Li X, et al. Abdominal radical trachelectomy: is it safe for IB1 cervical cancer with tumors Q 2 cm? Gynecol Oncol 2013;131:87-92.

10. Lintner B, Saso S, Tarnai L, et al. Use of abdominal radical trachelectomy to treat cervical cancer greater than 2 cm in diameter. Int J Gynecol Cancer 2013;23:1065-1070.

11. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study. Gynecol Oncol 1999;73(2):177-83.

12. Okugawa K, Kobayashi H2, Sonoda K, Kaneki E1, Kawano Y, Hidaka N, Egashira K, Fujita Y, Yahata H, Kato K. Oncologic and obstetric outcomes and complications during pregnancy after fertility-sparing abdominal trachelectomy for cervical cancer: a retrospective review. Int J Clin Oncol 2017;22(2):340-346.

13. Egashira K, Hiasa K, Yokota N, Kawamura T, Matshushita T, Okugawa K, Yahata H, Sonoda K, Kato K. Infertility after abdominal trachelectomy. Acta Obstet Gynecol Scand 2018 July.

14. Kim HS, Sardi JE, Katsumata N, Ryu HS, Nam JH, Chung HH, Park NH, Song YS, Behtash N, Kamura T, Cai HB, Kim JW. Efficacy of neoadjuvant chemotherapy in patients with FIGO stage IB1 to IIA cervical cancer: an international collaborative meta-analysis. Eur J Surg Oncol 2013;39(2):115-24.

15. Rydzewska L, Tierney J, Vale CL, Symonds PR. Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer. Cochrane Database Syst Rev. 2012 Dec 12;12:CD007406.

16. Chen Z, Shi Y, Wang S, Lu Q. Meta-analysis showing that early response to neoadjuvant chemotherapy predicts better survival among cervical cancer patients. Oncotarget 2017;8(35):59609-59617.

17. Li R, Lu ST, Si JG, et al. Prognostic value of responsiveness of neoadjuvant chemotherapy before surgery for patients with stage IB(2)/IIA(2) cervical cancer. Gynecol Oncol 2013;128:524-529.

18. Plante M. Bulky Early-Stage Cervical Cancer (2-4 cm Lesions): Upfront Radical Trachelectomy or Neoadjuvant Chemotherapy Followed by Fertility-Preserving Surgery: Which Is the Best Option? Int J Gynecol Cancer 2015; 25:722.

19. Robova H, Rob L, Halaska MJ, Pluta M, Skapa P, Strnad P, Lisy J, Komar M. High-dose density neoadjuvant chemotherapy in bulky IB cervical cancer. Gynecol Oncol 2013;128(1):49-53.

20. Laios A, Kasius J, Tranoulis A, Gryparis A, Ind T. Obstetric Outcomes in Women With Early Bulky Cervical Cancer Downstaged by Neoadjuvant Chemotherapy to Allow for Fertility-Sparing Surgery. A Meta-analysis and Metaregression. Int J Gynecol Cancer 2018;28:794-801.

21. Robova H, Halaska MJ, Pluta M, Skapa P, Matecha J, Lisy J, et al. Oncological and pregnancy outcomes after high-dose density neoadjuvant chemotherapy and fertility-sparing surgery in cervical cancer. Gynecol Oncol 2014;135:213–6.

22. Vercellino GF, Piek JM, Schneider A, et al. Laparoscopic lymph node dissection should be performed before fertility preserving treatment of patients with cervical cancer. Gynecol Oncol 2012;126:325-329.

23. Salvo G, Ramirez PT, Levenback CF, Munsell MF, Euscher ED, Soliman PT, Frumovitz M. Sensitivity and negative predictive value for sentinel lymph node biopsy in women with early-stage cervical cancer. Gynecol Oncol 2017 Apr;145(1):96-101.

24. Di Martino G, Crivellaro C, De Ponti E, Bussi B, Papadia A, Zapardiel I, Vizza E, Elisei F, Diestro MD, Locatelli L, Gasparri ML, Di Lorenzo P, Mueller M, Buda A. Indocyanine Green versus Radiotracer with or without Blue Dye for Sentinel Lymph Node Mapping in Stage >IB1 Cervical Cancer (>2 cm). J Minim Invasive Gynecol 2017;24(6):954-959.

25. Frumovitz M, Plante M, Lee PS, Sandadi S, Lilja JF, Escobar PF, Gien LT, Urbauer DL, Abu-Rustum NR. Near-infrared fluorescence for detection of sentinel lymph nodes in women with cervical and uterine cancers (FILM): a randomised, phase 3, multicentre, non-inferiority trial. Lancet Oncol 2018;19(10):1394-1403.

26. Cibula D, McCluggage WG. Sentinel lymph node (SLN) concept in cervical cancer: Current limitations and unanswered questions. Gynecol Oncol. 2018;151(3):438-443

27. Lissoni AA, Colombo N, Pellegrino A, Parma G, Zola P, Katsaros D, Chiari S, Buda A, Landoni F, Peiretti M, Dell'anna T, Fruscio R, Signorelli M, Grassi R, Floriani I, Fossati R, Torri V, Rulli E. A phase II, randomized trial of neo-adjuvant chemotherapy comparing a three-drug combination of paclitaxel, ifosfamide, and cisplatin (TIP) versus paclitaxel and cisplatin (TP) followed by radical surgery in patients with locally advanced squamous cell cervical carcinoma: the Snap-02 Italian Collaborative Study. Ann Oncol 2009;20(4):660-5.

28. Lorusso D, Petrelli F, Coinu A, et al. A systematic review comparing cisplatin and carboplatin plus paclitaxel-based chemotherapy for recurrent or metastatic cervical cancer. Gynecol Oncol 2014;133:117-123.

29. Kitagawa R, Katsumata N, Shibata T, Kamura T, Kasamatsu T, Nakanishi T, Nishimura S, Ushijima K, Takano M, Satoh T, Yoshikawa H. Paclitaxel Plus Carboplatin Versus Paclitaxel Plus Cisplatin in Metastatic or Recurrent Cervical Cancer: The Open-Label Randomized Phase III Trial JCOG0505. J Clin Oncol 2015;33(19):2129-35.

30. McCormack M, Kadalayil L, Hackshaw A, Hall-Craggs MA, Symonds RP, Warwick V, Simonds H, Fernando I, Hammond M, James L, Feeney A, Ledermann JA. A phase II study of weekly neoadjuvant chemotherapy followed by radical chemoradiation for locally advanced cervical cancer. Br J Cancer 2013;108(12):2464-9.

31. Salihi R, Leunen K, Van Limbergen E, Moerman P, Neven P, Vergote I Neoadjuvant chemotherapy followed by large cone resection as fertility-sparing therapy in stage IB cervical cancer. Gynecol Oncol 2015;139(3):447-51.

32. Schmeler KM, Frumovitz M, Ramirez PT. Conservative management of early stage cervical cancer: is there a role for less radical surgery? Gynecol Oncol 2011;120:321-325.

33. A Randomized Phase III Trial Comparing Radical Hysterectomy and Pelvic Node Dissection vs Simple Hysterectomy and Pelvic Node Dissection in Patients With Low-Risk Early Stage Cervical Cancer (SHAPE). https://clinicaltrials.gov/ct2/show/NCT01658930

34. Tseng JH, Aloisi A, Sonoda Y, Gardner GJ, Zivanovic O, Abu-Rustum NR, Leitao MM Jr. Less versus more radical surgery in stage IB1 cervical cancer: A population-based study of long-term survival. Gynecol Oncol 2018;150(1):44-49.

35. Plante M, Renaud MC, Sebastianelli A and Gregoire J. Simple Vaginal Trachelectomy. A Valuable Fertility-Preserving Option in Early-Stage Cervical Cancer. Int J Gynecol Cancer 2017;27(5):1021-1027.

36. Bentivegna E, Maulard A, Pautier P, Chargari C, et al. Fertility results and pregnancy outcomes after conservative treatment of cervical cancer: a systematic review of the literature. Fertil Steril 2016;106(5):1195-1211.

37. Bhatla N, Berek JS, Cuello Fredes M, Denny LA, Grenman S, Karunaratne K, Kehoe ST, Konishi I, Olawaiye AB, Prat J, Sankaranarayanan R, Brierley J, Mutch D, Querleu D, Cibula D, Quinn M, Botha H, Sigurd L, Rice L, Ryu HS, Ngan H, Mäenpää J, Andrijono A, Purwoto G, Maheshwari A, Bafna UD, Plante M, Natarajan J. Cancer of the cervix uteri. Int J Gynaecol Obstet. 2019 Jan 17.

38. Han K, Leung E, Barbera L et al. Circulating Human Papillomavirus DNA as a Biomarker of Response in Patients With Locally Advanced Cervical Cancer Treated With Definitive Chemoradiation. JCO Precision Oncology 2018;1-8.

39. Steenbergen R.D.M., Snijders P.J.F., Heideman D.A.M., Meijer C.J.L.M. Clinical implications of (epi)genetic changes in HPV-induced cervical precancerous lesions. Nat Rev Cancer 2014;14: 395–405.

40. Uijterwaal MH, van Zummeren M, Kocken M et al. Performance of CADM1/MAL-methylation analysis for monitoring of women treated for high-grade CIN. Gynecol Oncol 2016; 143:135–142.

41. Sood S, Patel FD, Ghosh S, Arora A, Dhaliwal LK, Srinivasan R. Epigenetic Alteration by DNA Methylation of ESR1, MYOD1 and hTERT Gene Promoters is Useful for Prediction of Response in Patients of Locally Advanced Invasive Cervical Carcinoma Treated by Chemoradiation. Clin Oncol (R Coll Radiol). 2015;27(12):720-7.

TABLE 1. Inclusion and Exclusion Criteria

Inclusion criteria for NACT:

- Age > 18 and ≤ 40 years old
- Eastern Cooperative Group (ECOG) performance status ≤ 2
- Invasive cervical cancer: adenocarcinoma, adenosquamous or squamous, Grade 1, 2 and 3
- Lymph-vascular space invasion (LVSI) allowed
- 2018 FIGO Stage IB2 measuring 2-4 cm (clinical exam and MRI)
- Pathologically negative pelvic nodes (based on pre-study lymph node dissection/SLN)
- Patients must be premenopausal
- Desire to preserve fertility potential

Inclusion criteria for fertility-preserving surgery:

- Completed the planned 3 cycles of NACT
- Achieved complete or partial response (<2 cm residual lesion) following NACT

Exclusion criteria for NACT

- Positive pelvic nodes
- Uterine corpus and extra-uterine extension (MRI)
- Lesions > 4 cm
- Other high-risk histology
- Pregnant women
- Patients who have had chemotherapy or radiotherapy for their cancer

Exclusion criteria for fertility-preserving surgery

- Patients unable to complete 3 courses of NACT
- Suboptimal response to NACT (≥2 cm residual lesion), stable disease or disease progression following 3 courses of NACT

TABLE 2. Primary objectives and endpoints

Primary objectives

- To evaluate the feasibility of preserving fertility in women with node negative, 2018 FIGO stage IB2 cervical cancer with lesions measuring 2-4 cm

Primary endpoints

- To assess the rate of functional uterus defined as successful fertility sparing surgery (FSS) and no adjuvant therapy.

TABLE 3. Secondary Objectives

- To evaluate the response rate based on RECIST 1.1 following neoadjuvant chemotherapy for patients with node negative FIGO 2018 stage IB2 cervical cancer
- To evaluate the surgical complication rate following fertility sparing surgery by the Clavien-Dindo classification of surgical morbidity
- To assess the rate of fertility sparing surgery
- To evaluate overall survival (OS) up to three years for patients who undergo neoadjuvant chemotherapy followed by fertility sparing surgery.

TABLE 4. Exploratory Objectives

- To evaluate the patient reported outcomes (PROSs) including quality of life (QoL), sexual health, anxiety/depression and reproductive concerns in women undergoing fertility sparing surgery after NACT for stage FIGO 2018 IB2 cervical cancer
- To evaluate ovarian function (FSH, estradiol, and AMH) following neoadjuvant chemotherapy and fertility sparing surgery.
- Rate of pregnancy during the follow-up period (3 years)
- To explore the possibility of disease monitoring by HPV circulating DNA (ctDNA/cfDNA) and hypermethylated DNA (hmDNA) measurements in cervical scrapes as applicable.

Figure 1. TRIAL SCHEMA