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

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ABSTRACT

Background There are limited data regarding the optimal management of pre-menopausal women with cervical lesions measuring 2–4 cm who desire to preserve fertility.

Primary objectives To evaluate the feasibility of preserving fertility.

Study hypothesis Neo-adjuvant chemotherapy will be effective in reducing the size of the tumor and will enable fertility-sparing surgery without compromising oncologic outcome.

Trial design Pre-menopausal women diagnosed with stage International Federation of Gynecology and Obstetrics (FIGO) IB2, 2–4 cm cervical cancer who wish to preserve fertility will receive three cycles of platinum/paclitaxel chemotherapy. Patients with complete/partial response will undergo fertility-sparing surgery. Patients will be followed for 3 years to monitor outcome. Patients with suboptimal response (residual lesion ≥2 cm) will receive definitive radical hysterectomy and/or chemoradiation.

Major eligibility criteria Patients must have histologically confirmed invasive cervical cancer, 2–4 cm lesion, by clinical examination and magnetic resonance imaging (MRI), negative node, and pre-menopausal (<40 years old). Following three cycles of neo-adjuvant chemotherapy, patients must achieve a complete/partial response (residual lesion <2 cm). Exclusion criteria include high-risk histology, tumor extension to uterine corpus/isthmus (as per MRI), and suboptimal response/progression following neo-adjuvant chemotherapy.

Primary endpoints Assess the rate of functional uterus defined as successful fertility-sparing surgery and no adjuvant therapy.

Sample size A total of 90 evaluable patients will be needed to complete the study.

Estimated dates for completing accrual and presenting results Expected complete accrual in 2022 with presentation of results by 2025.

Trial registration number Pending ethics submission.

INTRODUCTION

Almost 40% of women with cervical cancer are diagnosed between the ages of 20 and 44 years, with disease confined to the cervix in approximately 46% of cases.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 National Comprehensive Cancer Network (NCCN) guidelines.2 It is reassuring that a recent Surveillance, Epidemiology, and End Results (SEER) data analysis shows that uterine preserving surgery such as cone/trachelectomy is not associated with a higher risk of death compared with non-uterine preserving surgery (hysterectomy).3 However, in that analysis, risk factors independently associated with worsened outcome included lesion size >2 cm, adenosquamous histology, and lymph node positivity. Other series and literature reviews have also shown that the 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 cancers 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 procedure. The rates of fertility preservation vary significantly among different series, as does the rate of lymph node positivity and adjuvant treatments (10–45%).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 space invasion) 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 a permanent impact on quality of life and sexual health. For patients who preserve their fertility potential following abdominal radical trachelectomy, the fertility rate and obstetrical outcome appear to be reduced.4 A recent series of 151 abdominal radical trachelectomies confirmed that infertility treatments were frequently required following the procedure and that premature rupture of membranes and premature labor were frequently observed.12 The same group recently reported a high complication rate post-abdominal radical trachelectomy, resulting in infertility in up to 73% of cases.13

Neoadjuvant Chemotherapy followed by Fertility-Sparing Surgery

There are available data on the use of neoadjuvant chemotherapy 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 IB (the population of interest for this trial), IIb and IIId disease showed that neoadjuvant chemotherapy followed by surgery improves overall survival and progression-free survival compared with surgery alone and is associated with a 23% reduction in the risk of death.15 Other retrospective reviews and meta-analyses including patients with stage IB disease have also confirmed that neoadjuvant chemotherapy reduces the need for adjuvant radiotherapy, and is associated with decreased tumor size, lymph node involvement, and distant metastases.16–18 Globally the reported response rate to neo-adjuvant chemotherapy is in the region of 70%. Conversely, suboptimal response to neo-adjuvant chemotherapy appears to be an independent prognostic factor of poorer outcome.19

Considering the above, the concept of neoadjuvant chemotherapy was applied to young women who wished to preserve fertility in order to reduce the lesion size and subsequently allow fertility-sparing surgery. Review of five studies of neoadjuvant chemotherapy followed by fertility-sparing surgery showed a 71% response rate and better obstetrical outcome compared with upfront trachelectomy.20 However, patients with sub-optimal chemotherapy response were at higher risk of recurrence and death, suggesting that the lack of response to neoadjuvant chemotherapy is a marker of worse outcome.16–18 Bentivegna et al reviewed data from 17 series and case reports of neoadjuvant chemotherapy followed by less radical surgery, confirming good oncologic outcome in good chemotherapy responders.5 In addition, obstetrical outcome is favorable following that approach and appears superior compared with patients undergoing upfront radical trachelectomy.5,17 A very recent meta-analysis and meta-regression involving a total of 86 patients who underwent neo-adjuvant chemotherapy followed by fertility-sparing surgery confirmed that more radical surgery results in less favorable pregnancy outcome compared with less radical surgery.21

Unsettled Issues

▶ Lymph node staging

Even though neoadjuvant chemotherapy can potentially convert node positive to node negative patients14, 19–22 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 fertility-sparing surgery. Indeed, Vercellino et al reported a much higher recurrence rate in node-positive patients.23 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 lymph node mapping 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%).24 Indocyanine green is becoming the most widely used tracer for sentinel lymph node mapping, with excellent bilateral detection rate (91.7%) in patients with stage IB1 >2 cm, the group of interest in this study.25 A prospective randomized trial (FILM study) also confirmed the superiority of indocyanine green over blue dye for sentinel lymph node mapping.26 However, as pointed out recently by Cibula et al, there is currently no prospective evidence demonstrating the long-term oncologic safety of sentinel lymph node mapping alone in cervical cancer.27 Data from two large ongoing prospective trials (SENTIX and SENTICAL) are awaited.28, 29 Therefore, as part of this study, to ensure safety and quality control, patients are required to undergo complete pelvic lymph node dissection +/- sentinel lymph node mapping.

▶ Chemotherapy agents

Italian studies have shown that the combination of paclitaxel, ifosfamide, and cisplatin compared with paclitaxel and cisplatin is more effective in locally advanced cervical cancer, but is clearly more toxic.30 In addition, given that ifosfamide (alkylating agent) may potentially be gonadotoxic, most investigators have dropped ifosfamide from the combination. Lorusso et al conducted a systematic literature review and concluded that carboplatin represents a valid and less toxic alternative compared with cisplatin.31 A large Japanese randomized trial also showed that 3-weekly paclitaxel/carboplatin was not inferior to paclitaxel/cisplatin but was less toxic.32 More recently, weekly dose-dense paclitaxel 80 mg/m² with carboplatin AUC2 regimen has been studied in locally advanced cervical cancer with an objective response rate ranging between 68–87%.33 Interestingly, Sahili et al reported their experience with a slightly modified regimen (weekly paclitaxel 60 mg/m² with carboplatin AUC 2.7) with a good response rate but with limited alopecia, a potentially important consideration for young women in terms of quality of life.34 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 <2 cm, since the probability of parametrial extension in these cases is very low.35 The SHAPE trial is currently ongoing and prospectively compares radical hysterectomy versus simple hysterectomy in these low risk patients.36 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.37 There is a similar trend towards less radical surgery in women who wish to preserve fertility. Several series,
reviews and meta-analyses have shown excellent oncologic and improved obstetrical outcome following simple trachelectomy or cone versus radical trachelectomy.\textsuperscript{3, 6, 38, 39} Therefore, simple trachelectomy or large cone would appear to be adequate surgery in patients with complete/partial response (residual tumor <2 cm) following neo-adjuvant chemotherapy.

In summary, most of the available data on neo-adjuvant chemotherapy followed by fertility-sparing surgery come from limited small retrospective studies using a variety of treatment approaches. Thus, a standardized approach with regards to the optimal management of these patients is lacking. 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 become pregnant.

METHODS

Trial Design
CONTessa/NEOCON-F is a multi-center, prospective, single arm, phase II trial addressing the safety of neo-adjuvant chemotherapy followed by fertility-sparing surgery in young women with International Federation of Gynecology and Obstetrics (FIGO) 2018 stage IB\textsubscript{2} cervical cancer\textsuperscript{40} with lesions measuring 2–4 cm, who wish to preserve fertility.

Patients have to be under the age of 40 years and be pre-menopausal. Lesion size has to be assessed by pelvic magnetic resonance imaging (MRI) and physical examination. Squamous, adenocarcinoma, and adenosquamous histology, all grades, and lymphovascular space invasion are allowed. Pre-study entry criteria include a pelvic lymph node dissection ± sentinel lymph node 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 175 mg/m\textsuperscript{2} with carboplatin AUC6 every 3 weeks, or a weekly paclitaxel 80 mg/m\textsuperscript{2} and carboplatin AUC2 regimen. The use of cisplatin instead of carboplatin is allowed (paclitaxel 135 mg/m\textsuperscript{2} and cisplatin 50 mg/m\textsuperscript{2} every 3 weeks).

Following three cycles of neo-adjuvant chemotherapy, a clinical examination and pelvic MRI will be performed to assess tumor response. Patients with complete or partial response (lesion <2 cm) will then proceed to fertility-sparing surgery. The type of fertility-sparing surgery 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 fertility-sparing surgery based on risk factors identified on final pathological evaluation of the cervical specimen (margin status, lymphovascular space invasion, 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 2 and 3 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 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 Gynecologic Cancer Intergroup/Cervical Cancer Research Network (GCIG/CCRN) umbrella.

Participants and Outcomes
Inclusion and exclusion criteria are listed in box 1. Primary and secondary objectives and endpoints are listed in boxes 2 and 3, and exploratory objectives are listed in box 4.

Sample Size: Statistical Methods
If only 45% of patients at most are able to retain a functional uterus after the neo-adjuvant chemotherapy, the treatment would
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Box 3. Secondary objectives

- To evaluate the response rate based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 following neo-adjuvant 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 up to 3 years for patients who undergo neo-adjuvant chemotherapy followed by fertility-sparing surgery

be considered clinically not sufficiently interesting. We expect a success rate of at least 60%. Setting a one-sided α level to 0.025 and power to 80%, 90 women are required to test H0: ≤45% versus H1: p>60% using a one group χ² test.

Prior distribution of recurrence rate at 2 years is assumed to be β which corresponds to a mean of 10% and a standard deviation of 6.5%. The monitoring will start after five 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 the 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/).

If the stopping criteria are 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 are still met after the updated data are obtained, only then will the trial stop early.

The trial will be monitored by a Data and Safety Monitoring Board (DSMB) which will meet every 6 months to review all the data on the trial.

Quality of Life Studies

One of the objectives of this study is to evaluate the patient reported outcomes including quality of life, sexual health, anxiety/depression, and reproductive concerns in women undergoing fertility-sparing surgery after neo-adjuvant chemotherapy. Patients will complete patient reported outcome measures at baseline (before starting neo-adjuvant chemotherapy), before fertility-sparing surgery, and post-operatively (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 patient reported outcomes 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.

Correlative Studies: Disease Monitoring

- By human papillomavirus virus circulating DNA (ctDNA/ cfDNA)

Tumors release DNA into the circulation, where they can be measured non-invasively to assess disease burden. The majority of cervical cancers are caused by human papillomavirus; human papillomavirus 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 human papillomavirus DNA at baseline, and that detectable plasma human papillomavirus DNA at the end of chemoradiation is associated with inferior progression-free survival. We hypothesize that detectable plasma human papillomavirus DNA at the end of neo-adjuvant chemotherapy and after fertility-sparing surgery will be associated with inferior progression-free survival. Peripheral blood will be collected at different time-points during treatment and plasma will be isolated for the measurement of human papillomavirus 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 neo-adjuvant chemotherapy 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. DNA methylation markers have been shown to be valuable in the post-treatment monitoring of cervical intra-epithelial neoplasia (CIN) 2/3 lesions to identify women with an increased risk of recurrence. 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 been shown to be promising in the response prediction of chemoradiation in cervical cancer patients. We hypothesize that these markers can serve as predictors for response to neo-adjuvant chemotherapy and that recurrence of disease will be detected early by measuring these markers in cervical scrapes. Cervical scrapes will be collected before the start of chemotherapy, before fertility-sparing surgery, and during every follow-up visit for 3 years by ThinPrep. Targeted detection of multiple methylated genes will be performed by multiplex quantitative methylation-specific PCR (qMSP).

DISCUSSION

This phase II trial offers a well-standardized approach to the management of a very selected group of patients: young women...
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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 these cases per year, international collaboration will be key to the success of this trial, which is why it is being conducted under the leadership of GCIG/CCRN.

We expect that the majority of patients will successfully complete three cycles of the neo-adjuvant chemotherapy, 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 neo-adjuvant chemotherapy, 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 fertility-sparing surgery and be monitored for 2 and 3 years. Information on potential adjuvant therapy post fertility-sparing surgery will be collected as well as data on the 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 fertility-sparing surgery. However, in the event of risk factors identified on final pathology evaluation of the cervical specimen (positive/close margins, lymphovascular space invasion 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 ≥2 cm), stable disease or disease progression, fertility-sparing surgery 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 on patients with suboptimal response/progression on neo-adjuvant chemotherapy will be collected and may ultimately serve to help improve patient selection.

This trial will also provide important quality of life 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 hmDNA measurements in cervical scrapes.

In summary, we believe that this trial has the potential to influence current practice by providing clinicians with a standardized treatment approach to treat young women with larger cervical cancer

![Clinical Trial Diagram](http://ijgc.bmj.com)
lesions (2–4 cm) who wish to preserve fertility. We have designed a feasible, flexible, and simple protocol that will allow patient enrollment in different countries. Based on the parameters provided in this trial, we believe that the proposed treatment schema is safe (figure 1) and provides these young women the option of preserving their ovarian and reproductive function.

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


Funding The Princess Margaret Consortium is responsible for the funding of the Canadian sites’ accrual and for the overall data management. Each cooperative group is responsible for its own funding.

Competing interests None declared.

Patent consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

REFERENCES


