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)

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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.

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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

