"All accepted abstracts will be published in the JGO"

Abstract submission:
Open on June 1, 2021 - August 15, 2021
Abstract acceptance notification by:
September 15, 2021

Early Registration
Open: June 21, 2021
Close: September 30, 2021

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Sentinel lymph Node mapping versus systematic pelvic lymphadenectomy on the prognosis for patients with intermediate-high-risk Endometrial Cancer confined to the uterus before surgery: trial protocol for a non-inferiority randomized controlled trial (SNEC trial)

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ABSTRACT

Background: Sentinel lymph node (SLN) mapping has been recommended as an alternative staging approach to lymphadenectomy for apparent uterine-confined endometrial cancer (EC). However, the prognostic value of SLN mapping alone instead of systematic lymphadenectomy on EC patients remains unclear.

Methods: A multi-center, open label, non-inferiority randomized controlled trial has been designed to identify if SLN mapping alone is not inferior to pelvic lymphadenectomy on prognosis of patients with intermediate-high-risk EC clinically confined to the uterus. Eligible patients will be 1:1 randomly assigned to accept SLN mapping or pelvic lymphadenectomy. The primary endpoint is the 2-year progression-free survival (PFS). The second points are the 5-year PFS, 5-year overall survival, surgery-related adverse events and life quality. A total of 780 patients will be enrolled from 6 hospitals in China within 3-year period and followed up for 5 years.

Trial Registration: ClinicalTrials.gov Identifier: NCT04276532

Keywords: Sentinel Lymph Node; Lymphadenectomy; Endometrial Neoplasms; Uterus-Confined; Intermediate-High Risk; RCT
INTRODUCTION

Endometrial cancer (EC) is the most common gynecological cancer in developed countries, with an estimate of 61,880 new cases in the United States in 2019 [1]. Most new cases were ECs limited to the uterus and 10%-15% of them have lymph node metastases [2]. Recently, sentinel lymph node (SLN) mapping has been supported as an alternative staging technique to lymphadenectomy for apparent uterine-confined ECs [3-5], due to the high diagnostic accuracy, less injury, simple operative procedure and shorter hospitalization [6-11]. SLNs are the nodes at the highest risk with metastasis according to the drainage of the tumor [12]. Many studies have demonstrated the diagnostic advantages of SLN algorithm in early-stage EC [6], with a sensitivity of 91%-100% and a negative predictive value of 98%-100% [7-9]. The usage of pathological ultra-staging leads to better detection of lymph node metastasis compared with traditional lymphadenectomy [10,11].

Despite the verified diagnostic value, the impact of using SLN mapping alone instead of systematic lymphadenectomy on prognosis of EC patients remains unclear. On one hand, SLN sampling may bring risks to the prognosis because 1) SLN mapping may not remove all the metastatic lymph nodes: a large prospective cohort study (FIRES trial) on stage-I EC showed that among 35 SLN-positive patients, only 60% had disease limited to the SLN while 40% had additional positive nodes in their non-SLN specimens [9]; and 2) SLN mapping may miss isolated para-aortic lymph node metastasis, which also results in a poor outcome [13]. On the other hand, contrary findings reported no significant difference in median progression-free survival (PFS) between SLN and lymphadenectomy groups in patients with serous, clear cell, or carcinosarcoma subtypes of EC [14,15]. Recent National Comprehensive Cancer Network (NCCN) guideline also recommended SLN mapping for these high-risk patients [5], in whom the isolated para-aortic lymphatic metastasis was more common [16]. At present, there is no perspective evidence regarding the impact of SLN mapping alone compared with systematic lymphadenectomy in EC, particularly in the subtype of preoperatively obvious uterine-confined EC patients with intermediate-high risk of lymph node metastasis.

Thus, it is rationale and impulsive to conduct a randomized controlled trial, to assess whether SLN mapping can achieve a comparable prognosis and reduced postoperative morbidity compared with lymphadenectomy in patients with intermediate-high-risk EC clinically confined to the uterus. The findings of this trial will improve the understanding of the prognostic value of SLN mapping, while providing robust data for clinical guidance. The trial was registered with ClinicalTrials.gov (NCT04276532) and initiated on 13th February 2020.

MATERIALS AND METHODS

1. Objectives
The aim of this trial is to investigate the effect of SLN mapping on the prognosis of patients with intermediate-high-risk EC obviously confined to the uterus before surgery.

2. End points
The primary end point is the 2-year PFS. The 5-year PFS, 5-year overall survival (OS), adverse effects caused by surgery and quality of life (QOL) are secondary end points.
PFS is defined as the time interval between the date of operation after randomization and radiographic evidence of recurrence (local/distant) or second cancer or death (all causes). The diagnosis of recurrence was determined according to imagistic evidence of relapse (RECIST 1.1), whichever occur first. OS is defined as the time interval between the date of randomization and death (all cause); Health-related quality of life assessed before the surgery, and 6 months and 12 months after surgery, through a total score of a questionnaire designed for EC patients: EORTC-QLQ-C30 V3.0-EN24 [17]. Surgical morbidity within 30 days after surgery will be assessed according to the Clavien-Dindo classification [18].

3. Trial design and patients
Sentinel lymph Node mapping versus systematic pelvic lymphadenectomy on the prognosis for patients with intermediate-high-risk Endometrial Cancer confined to the uterus before surgery (SNEC) is a multi-center, open label, randomized controlled trial (NCT04276532). The study will conduct in the leading center, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, and 5 participating centers in China: Fudan University Shanghai Cancer Center, Shanghai; Cancer Hospital of The University of Chinese Academy of Sciences, Hangzhou; West China Second University Hospital, Sichuan University, Chengdu; Sun Yat-sen University Cancer Center, Guangzhou; and Zhongshan Hospital of Fudan University, Shanghai. All the centers are the member of Shanghai Gynecologic Oncology Group (SGOG) or South East Middle China Gynecological Oncology Group (CSEMGOG) for their high volume of gynecologic cancers and high quality of surgery.

4. Eligibility criteria
Eligible patients
The eligible patients were as follows: 1) Older than 18 years old; 2) Clinically diagnosed (by pre-surgical pathology and radiology) as primary endometrial cancer confined to uterus with intermediate-high risk factors: i) Disease limited to the uterus on image study (magnetic resonance imaging [MRI], computed tomography [CT] or ultrasound); ii) Including all histological types of endometrial cancer (endometrioid, serous, clear cell, carcinosarcoma, and undifferentiated carcinoma); not including uterine sarcoma; iii) Excluding low-risk endometrial cancer (endometrioid cancer grade 1-2 with pre-surgical endometrial lesion ≤2 cm and myometrial invasion <50%); iv) With one or more intermediate-high risk factors including: endometrioid endometrial cancer G3, myometrial invasion ≥50%, tumor size >2 cm, non-endometrioid endometrial cancer; cervical involvement; v) Diagnosis should be confirmed by at least two senior clinicians; 3) Be able to undergo staging surgery (Eastern Cooperative Oncology Group [ECOG] performance status 0– 1 or Karnofsky Performance Status [KPS] >70%).

Exclusion criteria
The exclusion criteria were as follows: 1) During pregnancy or perinatal period; 2) With malignancies other than endometrial cancer; 3) With history of important organs transplantation; 4) With immune diseases requiring taking immunosuppressants; 5) With severe mental illness or brain function disorders; 6) With history of drug abuse; 7) Allergic to contrast agent; 8) Still participating in other clinical trials; 9) Not willing to accept surgery or trial protocol; 10) Not eligible for surgery; 11) History of hysterectomy, chemotherapy, radiotherapy, or hormone therapy before the trial; and 12) History of retroperitoneal lymph node dissection for other reasons.

Withdrawal criteria
The withdrawal criteria were as follows: 1) Detecting extrauterine metastasis during surgery;
2) Significant enlarged lymph nodes are found during the surgery and lymph node metastasis are proved by rapid frozen-section pathology; 3) Detecting other malignancies except for EC during surgery; 4) Patients requiring withdrawal during the trial.

All patients should be pathologically confirmed as primary endometrial cancer by endometrial biopsy (aspiration biopsy, dilatation and curettage with or without hysteroscopy). Patients will undergo pelvic and abdominal enhanced MRI/CT to assess the presence of extrauterine metastases and involvement of pelvic and abdominal lymph nodes. Positron emission tomography-computed tomography (PET-CT) scan can replace the above imaging examination. For patients eligible for the enrollment, if postoperative pathology report shows extrauterine metastasis or lymph node metastasis, such patients will not be excluded from the study.

Pathologic diagnosis will be confirmed by two experienced gynecological pathologists according to the World Health Organization (WHO) pathological classification (2014). If their opinions differ, a seminar will be held in the pathological department for the final diagnosis. To ensure the quality of the pathological diagnosis, all the participating centers are well-recognized tertiary hospitals with high-volume gynecologic cancers, where high-quality pathological diagnosis are performed. The pre- and post-operative pathological diagnosis of all participants in the trial will be confirmed only in these centers. This study has been approved by the Ethics Committees of Obstetrics and Gynecology Hospital of Fudan University (2019-138), Fudan University Shanghai Cancer Center, Shanghai (SCCIRB2005217-20) and Zhongshan Hospital of Fudan University (SK2020-123). The ethical review at other 3 centers are in process. Before initiation of study procedures, written informed consent will be obtained from each patient regarding risks of treatments and agreement of using their clinical data for research purpose.

5. Randomization and masking
Randomization will be carried out separately in each center. A computer-based procedure of block randomization (SPSS for Mac, version 22.0; IBM Corp., Armonk, NY, USA) will be used for participant enrollment and randomization. The leading center (Obstetrics and Gynecology hospital of Fudan University) is the data center. The leading center will prepare the random assignment independently for each participating center by a computer-generated random number code. Details of the group allocations will be maintained in sequentially numbered, opaque, sealed envelopes prepared by a statistician with no clinical involvement in the trial. Before an individual is successfully enrolled, her treatment assignment will remain concealed. This trial will be open label: patients and study physicians were aware of treatment assignment. All the data will be input into a public database (REDCap, http://edc.easyclinical.org:9090/) that will be managed by a certain statistician to ensure the data accuracy and completement.

6. Treatment
After screening, eligible patients in each center will be randomly assigned (1:1) to receive SLN or pelvic lymphadenectomy (PLN) algorithm (Fig.1):
1) SLN group (arm 1): Total hysterectomy + bilateral salpingectomy ± oophorectomy ± omentum biopsy plus sentinel lymph node (SLN) mapping, or
2) PLN group (arm 2): Total hysterectomy + bilateral salpingectomy ± oophorectomy ± omentum biopsy plus pelvic lymphadenectomy (PLN) + para-aortic lymphadenectomy/para-aortic lymph node sampling. (+, with; ±, with or without; / , or)

The principles of surgery procedures and postoperative adjuvant therapies will follow the latest NCCN guidelines. Surgeries carried out by laparotomy, laparoscopy, or robotic surgery will be all accepted. All patients in this study will undergo a total hysterectomy plus bilateral salpingectomy with or without oophorectomy. The ovarian preservation is not recommended for participants in SNEC trial according to NCCN guideline. However, for patients who strongly ask for fertility preservation, ovarian preservation will be only considered in strictly selected premenopausal women with early-stage endometrioid cancer, normal-appearing ovaries, and no family history of breast/ovarian cancer or Lynch Syndrome. For patients with cervical involvement, the scope of surgery will be according to the latest NCCN guideline.

In PLN group, pelvic lymphadenectomy (LND) and para-aortic lymph node sampling/para-aortic LND should be carried out. Pelvic LND will be at least up to the level of bilateral common iliac arteries. The location of para-aortic lymph node biopsy depends on the doctor, but below the level of sub-mesenteric artery will be suggested. Para-aortic LND to the level of renal veins will be recommended although it is not routinely requested. Removal of pre-sacral lymph nodes will be not routinely requested, either. The lowest amount of removed pelvic and para-aortic lymph nodes are not required in this study. Pathological examinations on bilateral common iliac artery lymph nodes, para-aortic lymph nodes below the level of sub-mesenteric artery, and para-aortic lymph nodes above the level of the sub-mesenteric artery will be separately recorded.

All the surgeries will be performed by well-trained surgeons specified in gynecological oncology, with the certificate to perform the pelvic lymphadenectomy + para-aortic sampling or para-aortic lymphadenectomy. SLN mapping will be performed by experienced surgeons (who had independently and successfully completed SLN mapping on at least 20 cases). Colored dyes for SLN mapping including indocyanine green (ICG) (preferred), methylene blue or carbon nanotube will be accepted. SLN mapping should follow NCCN recommended protocol. A cervical injection with dye is suggested. Dye injection into uterus or intrauterine injection is also accepted. SLN algorithm for surgical staging of endometrial cancer must be strictly consistent with NCCN guideline. All SLNs should be processed using ultrastaging:

Endpoints:  
- Primary: 2 years PFS  
- Secondary: 5 years PFS/OS, adverse effects & QOL

Enrollment: 3 years  
Follow-up: 5 years

Fig. 1. Trial schema.
BS, bilateral salpingectomy; NCCN, National Comprehensive Cancer Network; O, oophorectomy; PLN, pelvic lymphadenectomy; QOL, quality of life; R, randomized; SLN, sentinel lymph node; TH, total hysterectomy.

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https://doi.org/10.3802/jgo.2021.32.e60
serial section with review of multiple hematoxylin and eosin-stained slides with or without cytokeratin IHC staining. Detailed information including the location, amount, macro-metastases, micro-metastases, and isolated-tumor-cell metastases of SLNs will be recorded in detail. To ensure that the surgery quality meets the requirements of SNEC trial, in each participating center, patients will be enrolled by a certain well-recognized senior gyn-oncologist. Furthermore, the surgery reports, surgery videos and pathology reports in each center will be checked regularly during the trial.

Postoperative adjuvant treatments will be strictly carried out following the latest NCCN guidelines. However, NCCN guideline provides multiple adjuvant-therapeutic options for some patients with risk factors, for example, vaginal brachy therapy (VBT) or observation are both acceptable for patients with G3 IA endometrioid endometrial cancer, as no best regimen has been confirmed. Hence, the investigators will make a decision strictly according to the latest NCCN guideline suggested options, such as, patient with endometrioid endometrial cancer G3 stage IA without any other risk factors can either choose VBT or observation according to the NCCN guideline. In addition, since there is no robust evidence yet to support a certain algorithm of postoperative treatment specific to isolated tumor cells (ITCs) or micro-metastases (MMs) status, patients with ITC will be only observed whereas patients with MMs will be treated as same as patients with lymph nodes metastasis. Any adverse event or complications during and after operation will be recorded in detail including: 1) intraoperative complications: vascular, bladder, intestinal, ureteral, obturator nerve or any unsuspected injury, bleeding greater than 1000ml, etc.; 2) postoperative complications within 30 days after surgery according to the Clavien-Dindo classification [18]. The mentioned complications that occur during postoperative adjuvant treatments will be evaluated to determine whether it is caused by surgery. Follow-up will be consistent with the latest NCCN guideline.

7. Statistical analysis
On the basis of data from previous studies [19], the 2-year PFS is expected to be 88% in the PLN group and 87% in SLN group. SLN would be considered as non-inferior to PLN if the 2-year PFS in SLN group is higher than 80%. The aim of the trial is to estimate the difference in 2-year PFS with sufficient precision and to exclude a clinically relevant absolute difference in efficacy. An accrual of 780 patients in 3 years will provide the study with adequate power (80%) to detect a clinically relevant absolute difference of 8% in 2-year PFS (88% vs. 80%) between both groups (one-sided test, a=0.025), with a rate of ≤10% including lost follow-up and withdrawal. Analyses will be done by intention to treat. Time-to-event analyses will be done with log-rank tests and Cox proportional hazards regression models with date of operation as starting point. The 2-year PFS, 5-year PFS and 5-year OS will be compared between SLN and PLN groups by logistic regression model. The rates of each surgery-related adverse event will be compared by $\chi^2$ test or Fisher's exact test. The t-test or Mann-Whitney U test will be used to compare the scores of life quality before the surgery, and 6 months, and 12 months after surgery between SLN and PLN groups. A p<0.05 will be considered significance. All statistical analyses will be done with latest version of SPSS.

8. Ethics and dissemination
The protocol has been approved by the Ethics Committees of Obstetrics and Gynecology Hospital of Fudan University and 2 collaboration hospitals. The ethics approval at other 3 hospitals will be obtained soon. The trial will be conducted according to the principles of the World Medical Association’s Declaration of Helsinki and in accordance with Good Clinical Practice (GCP) standards. The findings of the study will be published in a peer-reviewed journal.
9. Patients and public involvement

Patients and the public were not involved in the design of this trial.

DISCUSSION

The SNEC trial aims to assess whether SLN mapping can achieve non-inferior PFS to lymphadenectomy for patients with intermediate-high-risk EC clinically confined to the uterus. Also, the surgery-caused adverse-effects, life quality and long-term OS will be evaluated. To date, SLN algorithm has been recommended [3,5] for apparently uterine-confined ECs and non-endometrioid ECs as an alternative staging technique to lymphadenectomy. However, its prognostic value for these patients is not clear. Robust data from prospective and controlled studies are lacking. Thus, if our hypothesis is proven, our data will provide strong evidences for SLN mapping being accepted as a standard treatment, in order to improve the well-being for such patients.

In the SNEC trial we only focus on patients with intermediate-high-risk EC confined to uterus, to whom the SLN mapping are suggested to use by NCCN guideline [5]. We excluded patients with low-risk endometrial cancer (endometrioid endometrial cancer, grade 1–2 with pre-surgical endometrial lesion<2cm and myometrial invasion <50%) according to the algorithm for the surgical treatment of EC at Mayo Clinic, for their little benefit from either SLN or PLN approach [10,20]. Furthermore, our inclusion criteria still consist of the “pre-surgical tumor size >2 cm”, despite it is not considered as a risk factor for nodal assessment in current guidelines [3,5]. Up to date, clinical evidences only support the possibility of omitting surgical staging in EC patients with grade 1–2, endometrioid histology, myometrial invasion <50% and intraoperative tumor diameter ≤2 cm [10,20,21]. Patients with grade 1–2 endometrioid EC and tumor size >2 cm still had risks (11%) of lymph node dissemination and lymph node recurrence, for whom the lymph node assessment was suggested [21].

All the patients in control group will undergo both pelvic lymphadenectomy and para-aortic sampling/lymphadenectomy. Although para-aortic sampling/lymphadenectomy is not compulsory in NCCN guideline, the expert board of our trial strongly suggested at least para-aortic sampling should be performed as it provided important prognostic information that could affect the treatment decision.

In our trial the postoperative adjuvant therapies must follow the latest NCCN guidelines. NCCN guideline provides multiple adjuvant-therapeutic options for patients with risk factors, because no best regimen has been confirmed. Thus, for these patients the investigator will make decisions strictly according to the options that the latest NCCN guideline suggested, without specifying a certain regimen. Since our trial will take long time to finish (estimated 5 years or longer), meanwhile the NCCN guideline continues updating annually. If we specify a certain adjuvant therapy now, it might be no longer suitable a few years later with the changes in new version of NCCN guideline. Thus, we only require that the adjuvant therapies must follow the latest NCCN guideline to minimize the bias on prognosis, which is more realistic and ethically acceptable. Also, patients are always randomly assigned, in order to ensure the balance in adjuvant therapies between SLN and PLN groups during the updating in NCCN guideline.

The SNEC trial also accepts different colored dyes for SLN, although ICG is preferred. A recent prospective trial [22] reported a better detection on bilateral SLN by ICG than
blue dye alone in women with cervical and uterine cancers. In the SNEC trial, the dyeing method between each center can be different, but in the same center it is unified. As the randomization will be performed independently in each center, the bias generated by the dyeing methods could be minimized.

Some researchers may raise concerns about cervical injection may not achieve the same efficacy on detecting isolated para-aortic SLN as uterine/intrauterine injections for the SLN mapping. However, studies reported a similar anatomic distribution of SLN detected by cervical injection when compared with endometrial injection [23]. The recent FIRES trial also showed that even in high-grade EC patients who had been mapped at least one sentinel lymph node, no case of isolated para-aortic metastases was missing [9]. In the SNEC trial, like the dyeing method, injection location of SLN mapping is unified in the same center, although between each center it can be different. Also as mentioned earlier, the randomization will be performed independently in each center in order to reduce the bias in this respect.

Our non-inferiority randomized controlled trial requires a large sample size and collaboration with 6 centers. All centers are the member of SGOG or CSEMGOG for their high volume of gynecologic cancers and high quality of surgery. The SNEC trial has also registered in SGOG (SGOG-EC-01) and CSEMGOG (CSEM0016) for better multi-center cooperation. The accrual in the lead center (Obstetrics and Gynecology Hospital of Fudan University, Shanghai) has started in February 2020.

ACKNOWLEDGEMENTS

We thank Dr. Li-bing Xiang, Dr. Yu-lan Ren, Dr. Yang-long Guo, Dr. Fan Yang, Dr. Zhuo-zhen Sun, Dr. Chu-yao Zhang, Dr. Qin Zhu, Dr. Wen-yu, Shao, Dr. Wei-wei Shan, Ms Zhi-ying Xu for their efforts on this study.

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