SENTICOL III: International validation study of sentinel node biopsy in early cervical cancer. A GINECO, ENGOT and GCIG study.

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Background

- Sentinel node biopsy (SLN) is an alternative to pelvic lymphadenectomy (PLN). The false negative rate is <1% when "MSKCC Algorithm" is fulfilled [1]. The technique can detect isolated tumor cells (ITC) or micrometastases in 15 – 20 % of N0 patients, reveal SLN in unexpected areas in up 30% of cases and reduce short term lymphatic morbidity.
- However, despite all these data, SLN biopsy is not a standard of care in most guidelines. The only missing data is survival. No study demonstrated that patients assessed with SLN biopsy have the same prognosis than after a classical pelvic dissection. This information is mandatory before presenting SLN biopsy as a standard of care for early cervical cancer.
- In 2014, the GCIG brainstorming on cervical cancer pointed out the need for a validation study taking survival into account, giving birth to SENTICOL III (Melbourne, Nov 2014)[2].

Main eligibility criteria

- SENTICOL III is enrolling patients with squamous or adenocarcinoma of the cervix proven by biopsy or cone biopsy.
- Patients (age ≥ 18 years) with an early stage cervical cancer defined as FIGO stage Ia1 with lymphovascular invasion to IIa1, maximum diameter ≤ 40mm on MRI and node negative on imaging will be eligible to participate.

Primary objective

- The primary objective is a « **co-primary** » **objective regarding Disease Free Survival (DFS)** (non-inferiority of SLN vs SLN + PLN) and **Health Related Quality of Life (HR-QoL)** (superiority of SLN biopsy) in pN0 patients after SLN biopsy versus SLN biopsy + PLN.
- The hypothesis is that SLN biopsy alone provides similar DFS and better quality of life.
- Disease free survival (DFS) is defined as the time interval between randomization and physical or radiographic evidence of recurrence (local/distant) or second cancer or death (all causes) whichever occur first.
 - HR-QoL of patients is assessed with EORTC QLQC 30 and QLQ-CX24 with 3 targeted dimensions: pain, global health score and physical functioning scores at 3 years.

Secondary objectives

- Secondary objectives are outcome of patients with isolated tumor cells and micrometastasis, evaluation of mapping with indocyanine green, surgical morbidity and mortality, other dimensions of health related Quality of life (QLQ-C30+QLQ-CX24) and longitudinal analysis of all collected dimensions, positive and negative predictive values of SLN biopsy overall survival, overall survival, recurrence free survival and lymphatic and lower limb complications.
- A cost analysis will be performed in some countries.

Fig. 1. SENTICOL III Study design

Translational research

- Each site participating to the SENTICOL III study will participate to a tumor and blood sample collection. The translational research program will be performed in a second step.
- Biological samples will be used for exploratory work to search for biological predictors of relapse in "low risk" early cervical cancer as detailed below:

Time of the study	Type of sample	Optional/mandatory
Inclusion	<ul style="list-style-type: none"> Archival tumor sample from cervix biopsy or part of the conisation, Blood sample (20 mL) (Only for French sites) 	Mandatory
Surgery	<ul style="list-style-type: none"> SLN sample from the surgery, nSLN sample from the surgery 	Mandatory
Disease progression	<ul style="list-style-type: none"> Tumor samples, Blood sample (20 mL) (Only for French sites) 	Optional and if available

References

- Altgassen C, Hertel H, Brandstädt A, Köhler C, Dürst M, Schneider A; AGO Study Group. Multicenter validation study of the sentinel lymph node concept in cervical cancer: AGO Study Group. J Clin Oncol 2008; 26: 2943-2951
- Sagae S, Monk BJ, Pujade-Lauraine E, Gaffney DK, Narayan K, Ryu SY, McCormack M, Plante M, Casado A, Reuss A, Chávez-Blanco A, Kitchener H, Nam BH, Jhingran A, Temkin S, Mileskin L, Berns E, Scholl S, Doll C, Abu-Rustum NR, Lecuru F, Small W Jr; participants of the Gynecologic Cancer InterGroup Cervix Cancer brainstorming day. Advances and Concepts in Cervical Cancer Studies: A Road Map for the Future. Int J Gynecol Cancer. 2016 Jan;26(1):199-207.

Study design, randomization and stratification

- SENTICOL III is an international, prospective, randomized, multicenter, **single blind trial**.
- Up to 950 patients will be randomized prospectively (by minimization with a random component of 20%) using an Interactive Web Response System in a 1:1 ratio.
- Only patients with negative frozen section on SLN will be randomized** into one of the following arm:
 - Arm A (experimental arm):** patients will have a **SLN dissection only**. The radical hysterectomy or trachelectomy will be done.
 - Arm B (reference arm):** patients will have a **SLN biopsy and a systematic pelvic dissection**. The radical hysterectomy or trachelectomy will be done.
- Randomization will be stratified by:
 - Center,
 - Stage of the disease (FIGO stage)
- Patients pN1 will be followed in a separate cohort** to record their outcome according to the size of metastasis (isolated tumor cells, micrometastasis and macrometastasis).

Statistical considerations

- DFS:** We aim to demonstrate a non-inferiority of SLN biopsy vs SLN biopsy + PLN with a non-inferiority margin of 5% (80 vs 85%, HR = 1.373), with a unilateral alpha error of 5%, a power of 80%, and with 5 years of follow-up. 900 patients should be randomized in 3 years to observe the required 263 events.
- An interim analysis will be planned when at least 132 events will be observed
- HR-QoL:** we target 3 HR-QoL dimensions of the EORTC QLQ-C30 and QLQ-CX24: global health, pain and physical functioning. We aim to demonstrate at 3 years a superiority of at least one of the 3 targeted dimensions without significant deterioration in at least one with a minimal clinically important difference in mean score of at least 5 points (SD: 20), and a bilateral alpha type one error of 0.016.

Study calendar

- Sites number:** 300, including 50 in France
- Patients number :** 950, including 200 in France
- Study start:** Q2 2018 in France, Q3 2018 in the other countries
- Accrual period:** 36 months,
- Follow-up period:** 5 years,
- Total study duration:** 8 years.

Conclusions

- SLN biopsy oncologic safety has never been demonstrated, since no specific study has been developed to ensure that patients categorized as pN0 with the SLN technique have the same survival as patients selected by a classical pelvic dissection.
- SENTICOL III aims to demonstrate that SLN biopsy alone provides similar DFS and better quality of life than SLN biopsy + PLN.