STATEC

Selective Targeting of Adjuvant Therapy for Endometrial Cancer

Florine Eggink

National kick-off meeting

April 17th 2018

Disclosures

(potentiële) belangenverstrengeling	Geen
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Geen
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk …	• • • •

STATEC

- “A randomised trial of non-Selective versus selective adjuvant Therapy in high risk Apparent sTage 1 Endometrial Cancer”

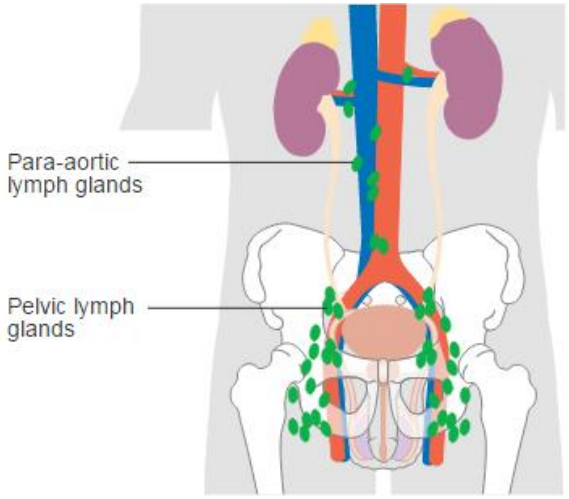
- Initiated by the University College London, United Kingdom

Background

- Treatment for endometrial cancer patients
  - Hysterectomy + BSO
  - In high-intermediate/high risk patients:
    - Adjuvant therapy (radio/chemotherapy)
    - In some hospitals: staging including omentectomy and lymphadenectomy
- Why perform lymphadenectomy?
  - Staging, risk stratification, guide choice of adjuvant therapy?
  - Removal of micrometastases, improve survival?

Pelvic + Para-aortic Lymphadenectomy

- Prevalance of metastases to LN's in HR population: ~15-20%
- When pelvic nodes + → PA nodes + in 47%
- Isolated PA nodes in 16%



Disadvantages to lymphadenectomy

- Compared to standard surgery:
  - Higher risk of surgery-related morbidity
    - Lymphocysts
    - Lymphedema
  - Increased operating time
  - Increased length of stay at hospital

LEGS trial

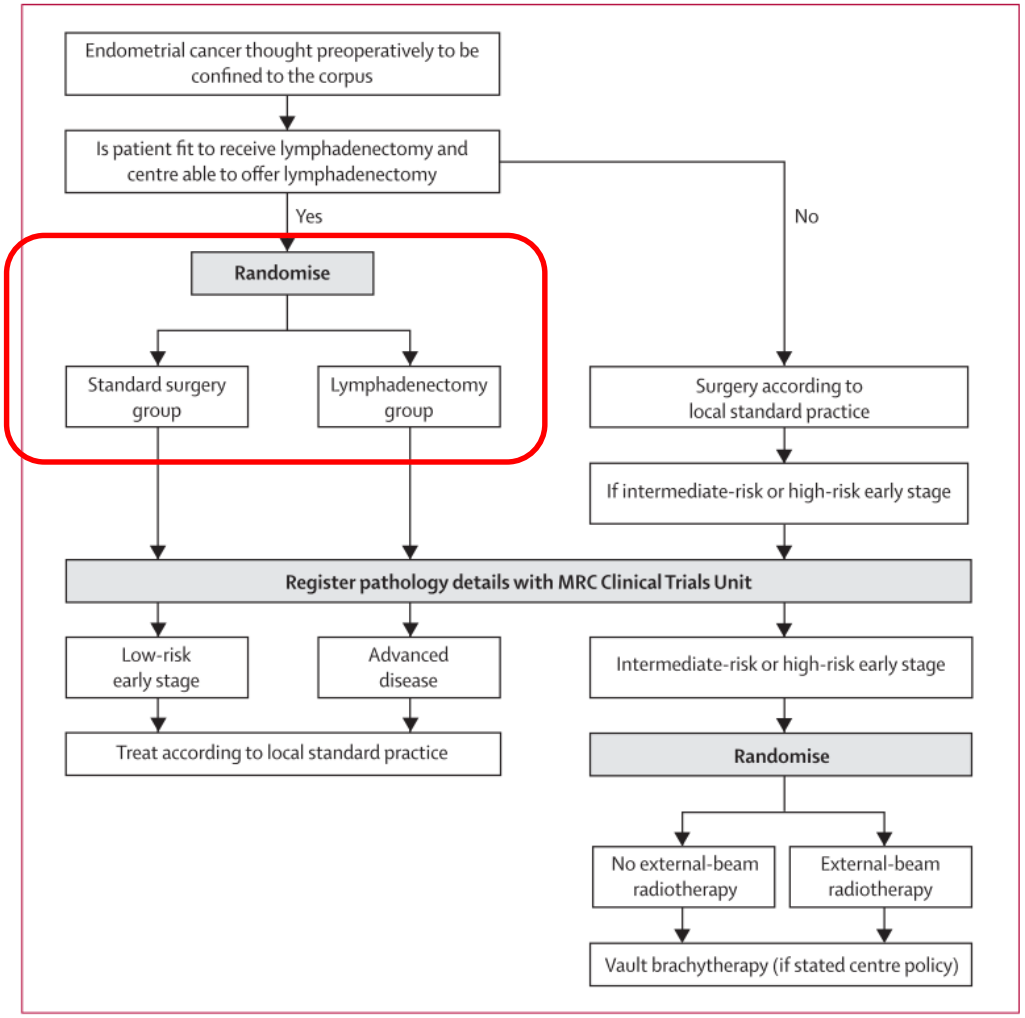
- Lymphoedema in gynecological cancer study
- Prospective longitudinal study
- N=408 women with surgical treatment for gynecological cancer
- Pre-surgery:
  - 15% self-reported lymphoedema
  - 27% measured lymphoedema
- 24-mths post surgery:
  - New self-reported lymphoedema 45%
  - New measured lymphoedema 37%
  - 75% presented at 12-mths post surgery
  - 60% persistent lymphoedema

Hayes et al,
Gynecol Oncol 2017

Trials aimed at therapeutic value of lymphadenectomy

- Study the impact of lymphadenectomy on survival
- Node status did not impact choice of adjuvant therapy

ASTEC trial

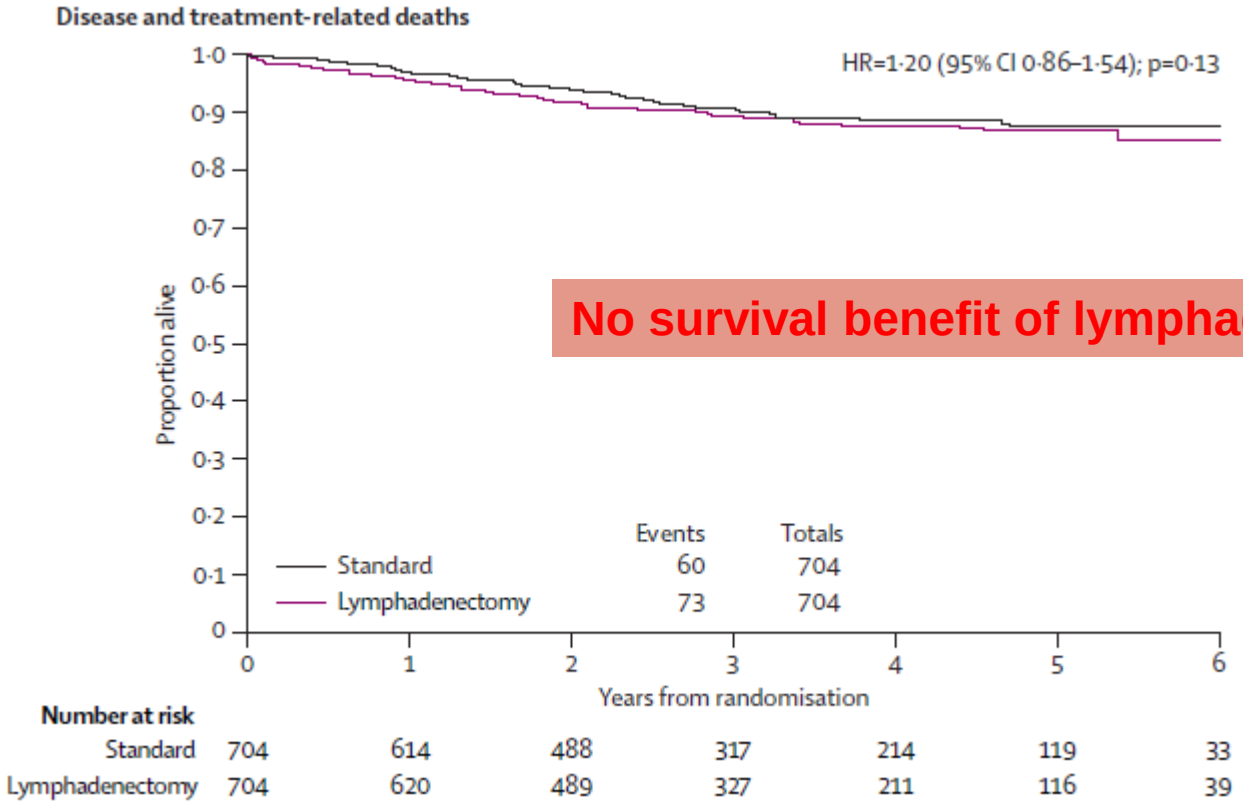


N=1408
Early stage EC

704 Standard surgery
704 Pelvic lymphadenectomy

Kitchener et al,
Lancet 2009

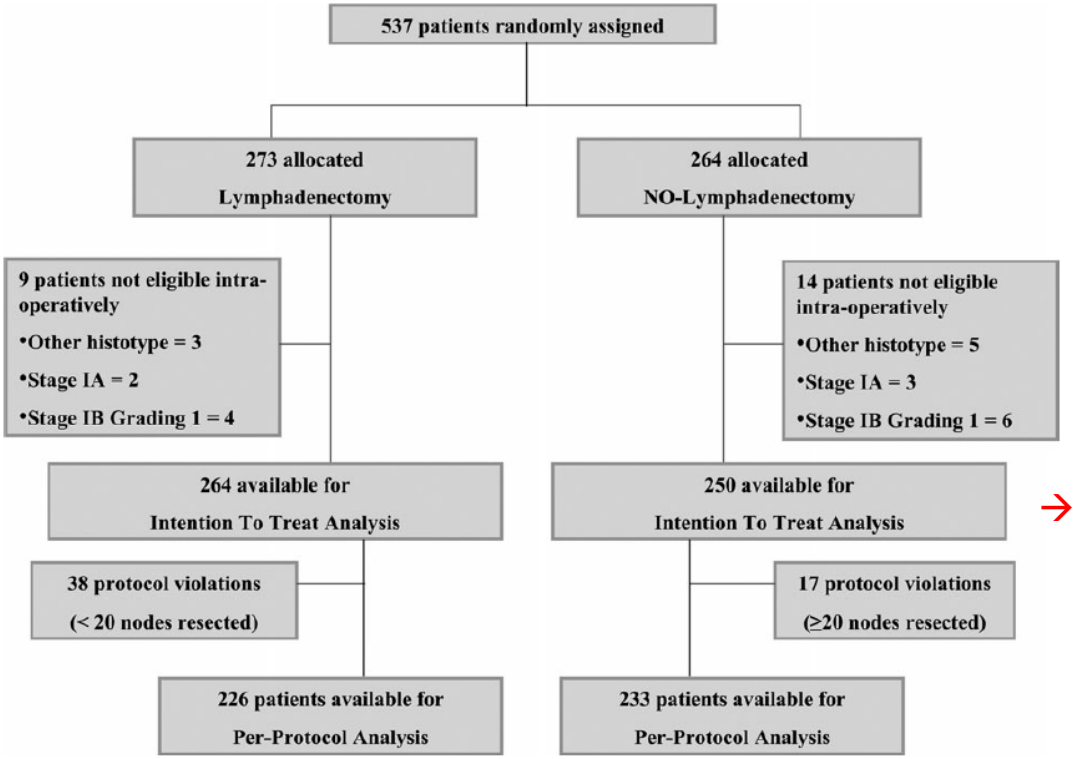
ASTEC trial



No survival benefit of lymphadenectomy

Kitchener et al, Lancet 2009

Panici trial



→ N=514

- Systematic Pelvic Lymphadenectomy vs No Lymphadenectomy in Early-Stage Endometrial Carcinoma: Randomized Clinical Trial

- Pelvic lymphadenectomy: removal of >20 nodes
- Para-aortic node resection at discretion of surgeron (26% in L arm, 2% NL arm).

Panici et al,
JNCI 2008

Panici trial

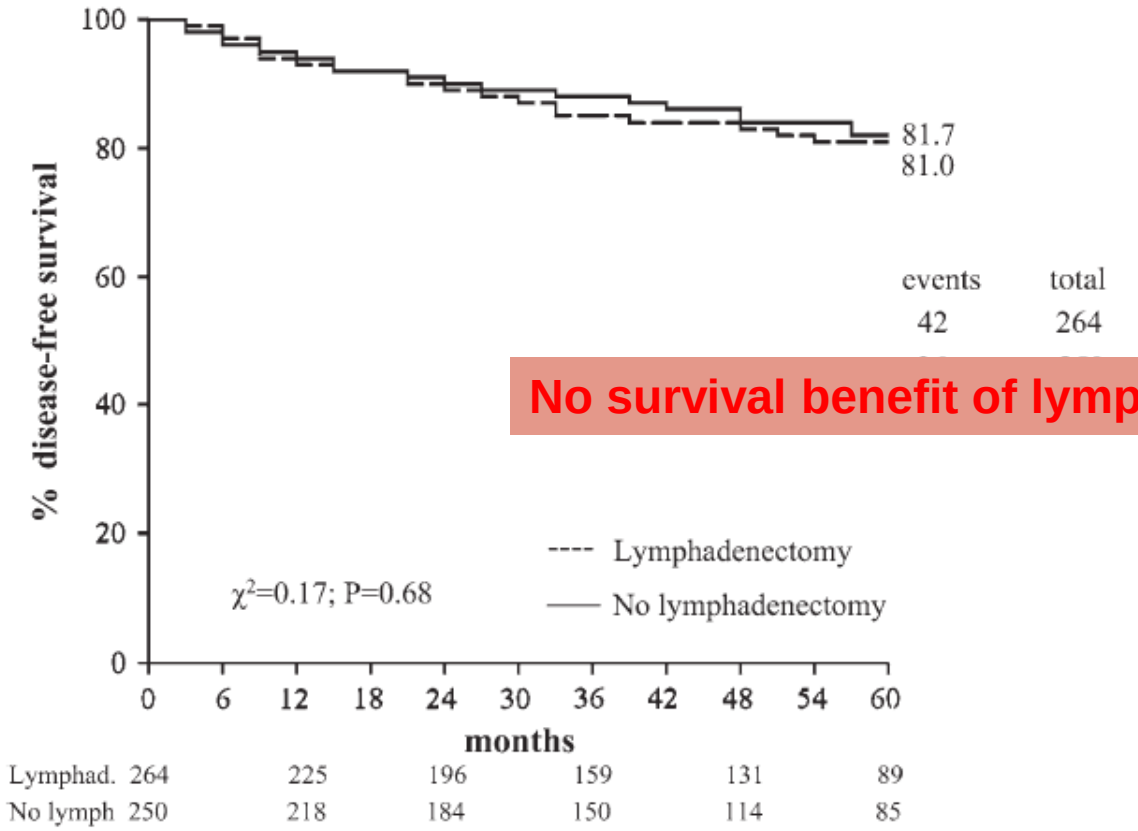


Figure 2. Disease-free survival for patients with clinical early-stage endometrial cancer undergoing systematic pelvic lymphadenectomy (Lymphad.) vs those undergoing resection of bulky lymph nodes only (No lymph). All statistical tests were two-sided.

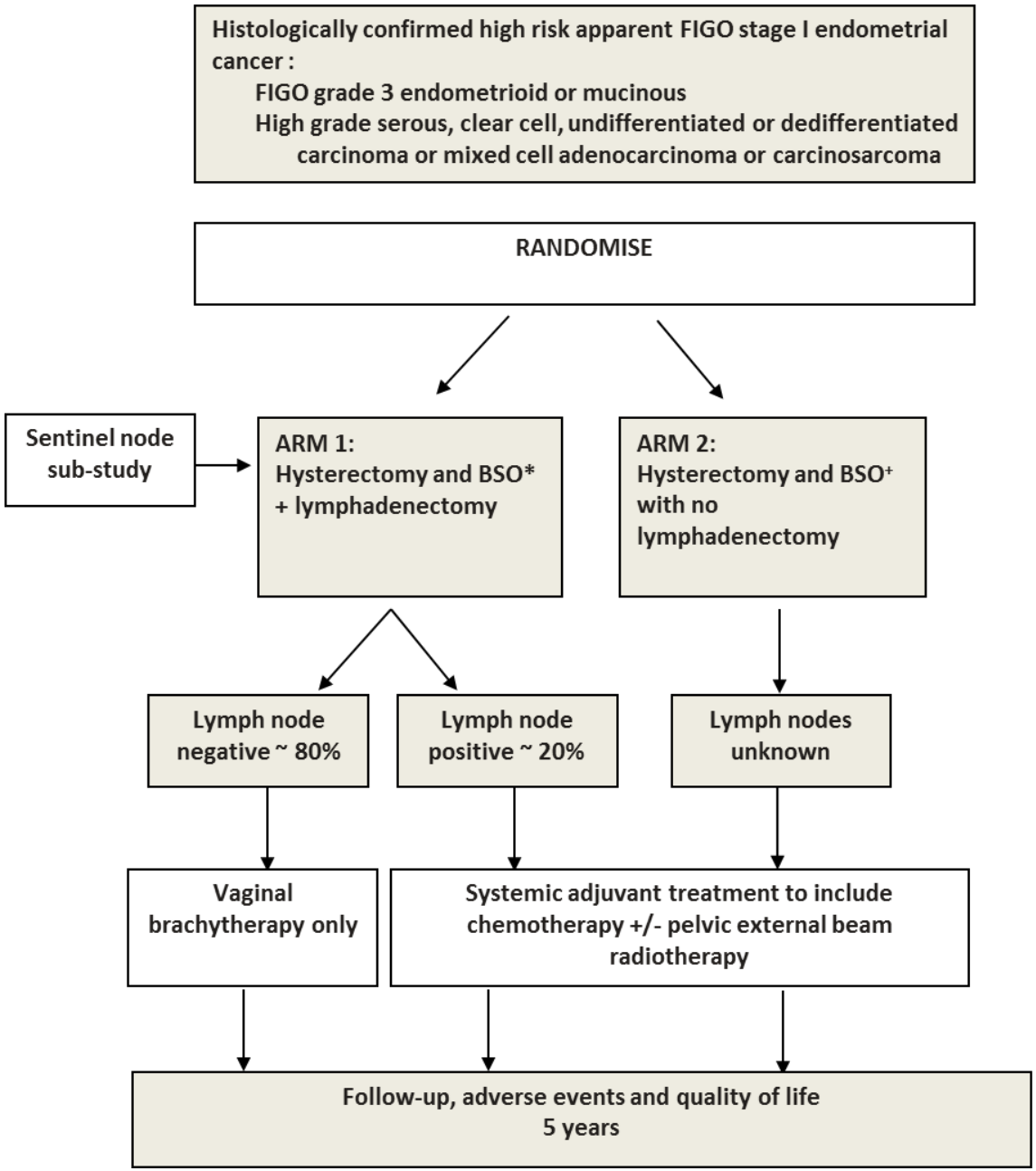
Panici et al, JNCI 2008

Limitations of these studies

- Did not select high risk patients only
- Variation in extent of lymphadenectomy
  - ASTEC: 35% <10 nodes removed
  - Panici: Lymphadenectomy defined as >20 nodes
  - Para-aortic lymphadenectomy left to discretion of surgeon
- Node status did not directly impact adjuvant therapy
- QoL was not sufficiently evaluated

Hypotheses STATEC

- Lymphadenectomy is not independently therapeutic
- Lymphadenectomy, used to restrict adjuvant therapy to node positive women, results in a non-inferior survival as compared to adjuvant therapy given to all women with high risk apparent stage I endometrial cancer
- Tailoring adjuvant treatment based on node status may limit adverse events with non-inferior survival
- Sentinel node biopsy may be as effective as full lymphadenectomy to triage patients to adjuvant treatment



* Option to be randomised ≤ 28 days after hysterectomy and BSO

International trial

- N=1720 patients minimum

- United Kingdom
- Australia
- New Zealand

- The Netherlands (expected to include ~50 patients/year)
  - 13 hospitals expected to participate
  - NL will follow UK protocol + DGOG specific appendix

Participating hospitals in NL

Hospital	Principal Investigator
Catharina Ziekenhuis	Dr. R.L.M. Bekkers
Elisabeth-Tweesteden Ziekenhuis	Drs. M.C. Vos
Haaglanden Medisch Centrum	Dr. L.C.F. Haans
HAGA Ziekenhuis	Dr. B.W.J. Hellebrekers
Isalaklinieken	Drs. A.J. Kruse
Leiden University Medical Center	Dr. C.D. de Kroon
Maastricht University Medical Center	Dr. S. Lambrechts
Medisch Spectrum Twente	Dr. N. Reesink-Peters
Nederlands Kanker Instituut- Antoni van Leeuwenhoek Ziekenhuis	Dr. J.W. Trum
Reinier de Graaf Gasthuis	Dr. A. Baalbergen
University Medical Center Groningen	Prof. Dr. H.W. Nijman
University Medical Center Utrecht	Dr. R.P. Zweemer
Zuyderland Ziekenhuis	Drs. M.J.A. Engelen

Outcomes

- Primary:
  - Overall survival (non-inferiority trial)
- Secondary:
  - Disease free survival, endometrial cancer specific survival
  - Cost effectiveness
  - Surgical adverse events (acute and late)
  - Quality of life
- Side studies:
  - Value of sentinel lymph node assessment
  - Translational work on STATEC samples

Organisation of trial in NL

- Country Coordinating Centre: UMCG
- Principal Investigator: Prof. Dr. Hans W. Nijman
- Funding for datamanagement: KWF

- Local trial coordination, data management, monitoring: IKNL
  - STATEC trial coordinator at IKNL: Hilde Dijcker

- Coordination of sentinel node sub-study:
  - Dr. Ronald Zweemer
  - Drs. Eline Reynaers

Surgical QA

- Surgical Imaging QA of all Arm 1 patients (the lymphadenectomy arm).
  - *No photographic images are required for Arm 2 (no lymphadenectomy arm).*
- Local site surgeons will be required to obtain photographic images of the surgical site after lymph node dissection + upload images to trial database server
  - 5 locations: L pelvic (LP), R pelvic (RP), Pre sacral (PS), L para aortic (PAL), R para aortic (PAR)
- A Surgical Imaging QA sub-group of the trial management group (TMG) will review these images and provide site feedback.
- See QA manual for more information

Trial adjuvant treatment

- 3 options in protocol:
  1. CT+EBRT schedule as used in PORTEC3
     - EBRT combined with 2 cycles cisplatin followed by 4 cycles of carboplatin+paclitaxel
     - Optional VBT boost
  2. Sequential CT and EBRT
     - 4-6 cycles CT before or after EBRT
  3. CT without EBRT
- Meer informatie in STATEC adjuvant treatment guidance document

QoL and Lymphedema substudy

- Questionnaires, logistics to be discussed by Hilde Dijcker, IKNL

Sentinel lymph node side study

- To be discussed by Ronald Zweemer, UMCU

Translational research in NL

- In NL no collection of translational blood samples
- Translational tissue samples:
  - FFPE tissue from surgery:
    - 1 block tumor from hysterectomy and BSO specimen
    - 1 block tumor from lymph nodes (if randomized to lymphadenectomy)
- All samples to be labelled with the patient trial ID and date of sample collection.
- Storage at clinical sites until further notice

Insurance

- All sites responsible for their own liability insurance
  - ‘aansprakelijkheids verzekering’
- UMCG holds an insurance for all trial subjects
  - ‘proefpersonen verzekering’

Current status

- Funding UK/AUS/NZ/NL ✓
- UK:
  - Open and recruiting
- Aus/NZ:
  - Open and recruiting
- NL:
  - Ethical approval ✓
  - Final preparations: local approvals, contracts with participating hospitals, etc.

STATEC NL team

- STATEC NL general (statec@og.umcg.nl)
  - Hans Nijman
  - Florine Eggink
  - Natascha de Lange
- STATEC SLN side study
  - Ronald Zweemer
  - Eline Reynaers
- Local trial coordination, data management, monitoring: IKNL (trialbureau@iknl.nl)
  - Hilde Dijcker
  - Ine Leenen

Questions?

Suggested Trial adjuvant treatment STATEC NL

- Lymphadenectomy group:
  - LN neg: VBT
  - LN pos (FIGO stadium IIIC): treatment according to PORTEC3 scheme
    - EBRT+2 cycles concurrent chemotherapy (Cisplatin) and 4 cycles chemotherapy (carboplatin + paclitaxel). Optional VBT boost in case of cervical involvement.
    - OR 4-6 cycles chemotherapy (carboplatin + paclitaxel) before/after EBRT

- No lymphadenectomy group:
  - Treatment according to local multidisciplinary team, based on definitive pathology features. For example:
    - FIGO I-II endometrioid: EBRT
    - FIGO IB-II serous/clearcell: EBRT with/without chemotherapy (PORTEC3 scheme)
    - FIGO IIIA-IIIB endometrioid/serous/clearcell: EBRT + chemotherapy (PORTEC3 scheme)