Selective Targeting of Adjuvant Therapy for Endometrial Cancer

Florine Eggink
National kick-off meeting
April 17th 2018
## Disclosures

<table>
<thead>
<tr>
<th>(potentiële) belangenverstrengeling</th>
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<tr>
<td>Voor bijeenkomst mogelijk relevante relaties met bedrijven</td>
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<tr>
<td>• Sponsoring of onderzoeksgeld</td>
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<td>• Honorarium of andere (financiële) vergoeding</td>
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<td>• Andere relatie, namelijk …</td>
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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

- Prevalence 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

- 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 surgeon (26% in L arm, 2% NL arm).

Panici et al, JNCI 2008
Panici trial

No survival benefit of lymphadenectomy

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
Histologically confirmed high risk apparent FIGO stage I endometrial cancer:

- FIGO grade 3 endometrioid or mucinous
- High grade serous, clear cell, undifferentiated or dedifferentiated carcinoma or mixed cell adenocarcinoma or carcinosarcoma

RANDOMISE

Sentinel node sub-study

ARM 1: Hysterectomy and BSO* + lymphadenectomy

- Lymph node negative ~ 80%
  - Vaginal brachytherapy only

- Lymph node positive ~ 20%
  - Systemic adjuvant treatment to include chemotherapy +/- pelvic external beam radiotherapy

ARM 2: Hysterectomy and BSO+ with no lymphadenectomy

- Lymph nodes unknown

Follow-up, adverse events and quality of life 5 years

* 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

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