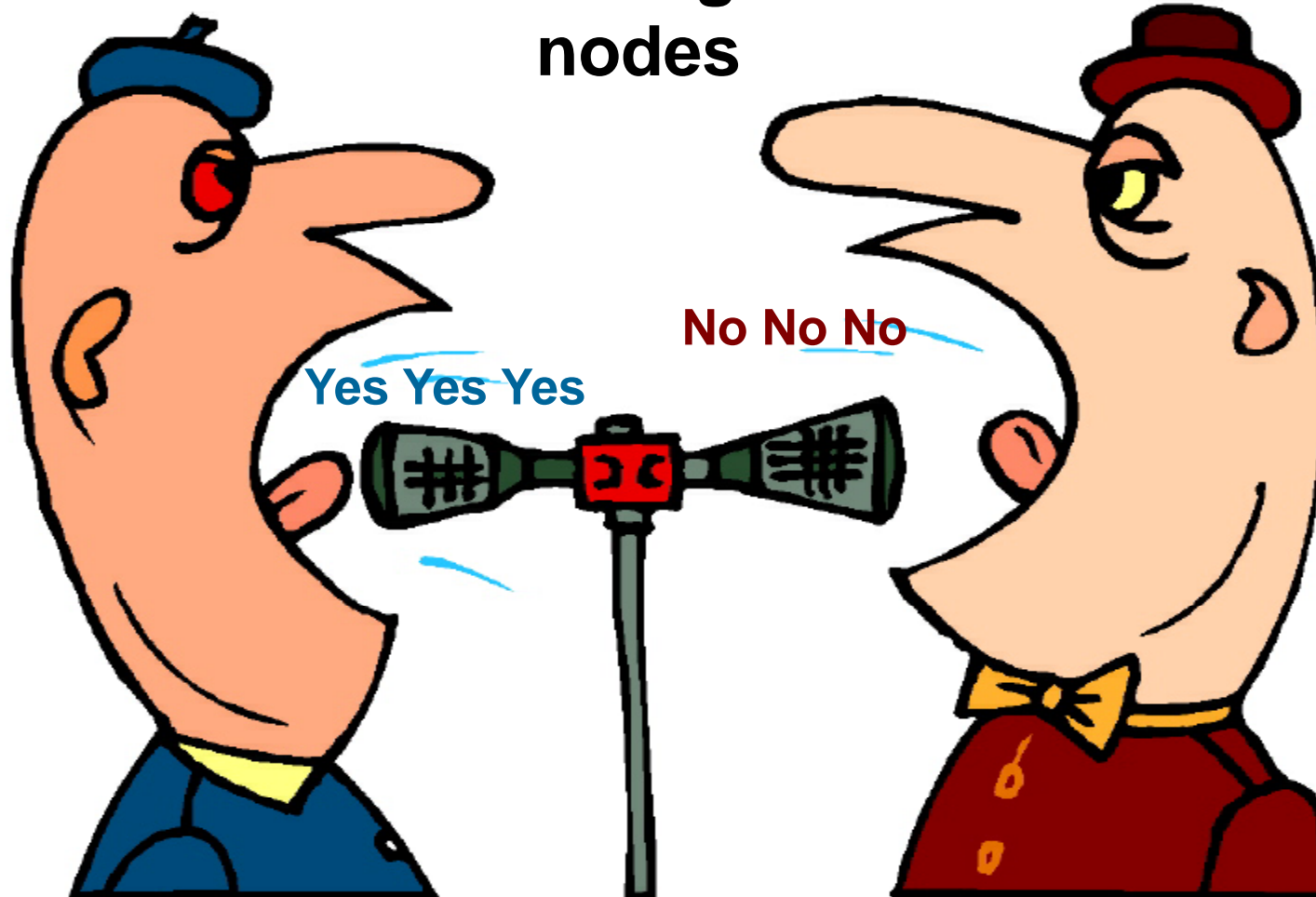


# Risk adapted approach to surgical staging in early endometrial cancer

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# Doing nodes




1957-----2008

# Lymphadenectomy: The debate

## Pro

- True extend of disease (full staging)
  - Better counseling of patients
  - Proper selection of adjuvant therapies
- Improvement of survival (therapeutic)

## Against

- Morbidity and complications
  - Strong relation with classic risk factors (PORTEC → RT)
  - No proven advantage (no level 1 evidence)
- 

## **--Guidelines--**

# **Full pelvic and para-aortic lymphadenectomy for the staging of endometrial cancer**



- International Federation of Gynecology and Obstetrics (FIGO)
- Society of Gynecologic Oncology (SGO)
- National Comprehensive Cancer Network
- American College of Obstetricians and Gynecologists

# Guidelines

*If you want to do 'the right job' you must follow the guidelines !*

*All patients must be surgically staged or they are being inadequately or improperly treated*



# The Netherlands



# Holland and guidelines



# Position The Netherlands (1970 – 2000)

**No** (lymphnode) staging in early stage endometrial cancer

- Overall 5 year survival > 85%
- No 'proven' therapeutic effect of node dissection
- 90 - 95% of fully staged patients will be node negative
- RT by risk factors (age, grade and infiltration depth)
- Increased morbidity of node dissection

# Treatment of EC should be risk based

- **PREVENT OVERTREATMENT OF LOW RISK PATIENTS**
  - **IMPROVE OUTCOME OF HIGH RISK PATIENTS**
- 

# Major prognostic factors → **risk !**

- stage
- age
- histological type
- grade
- depth of myometrial invasion
- lymph-vascular space invasion



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- stage
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# Three 'histological' types of endometrial cancer

Type 1: Endometrioid **in hyperplasia**

*Estrogen related, + nodes < 5%, good survival*

Type 2: Endometrioid **in atrophic endometrium**

*Non estrogen related, + nodes 5-15%, intermediate survival*

Type 3: Non endometrioid histology

*Non estrogen related, + nodes > 15%, poor survival*

# Major prognostic factors → **risk !**

- stage
- age
- histological type
- **grade**
- **depth of myometrial invasion**
- lymph-vascular space invasion

# Lymph node metastases (GOG-33)

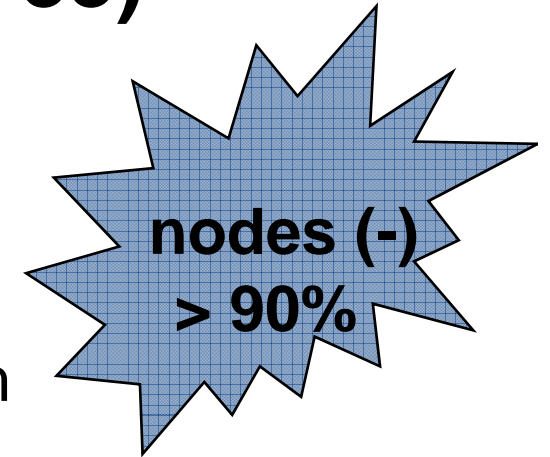
*N=625 clinical stage I*

- 11% lymph node involvement
  - » 9% pelvic; 5% aortic; 3% both  
*(7% pelvic; 4% aortic)*
  
- Risk of pelvic node involvement:
  - » outer 1/3 invasion: 25%
  - » grade 3: 18%
  - » grade 3 and deep invasion: 34%

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# Risk groups

- Low risk:
  - Stage IA or IB, grade 1 or 2
  - Non-serous and non-clearcell
- Intermediate risk
  - All others
  - Non serous and non-clearcell
- High risk
  - Stage IC, grade 3
  - Serous and clearcell

# Major prognostic factors → **risk !**

- stage
- age
- histological type
- grade
- depth of myometrial invasion
- lymph-vascular space invasion

# Lymph-vascular space invasion (LVSI)

- N=239 surgically staged
- Predictor of nodal disease; 5-fold risk for N+ ( $p=0.001$ )
- LVSI independent prognostic factor for relapse: 39 vs 19%,  $p<0.0001$
- Both with and without lymphadenectomy

# Evidence for or against surgical staging

*(Over the past 30 years)*

- Many retrospective single institutional studies *Level 3/4*
- Some retrospective national or multi institutional studies *Level 3/4*
- Numerous authority based statements *Level 4+*
- One prospective randomised study (ASTECC) *Level 2*

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**Poor result !!!**

# Lymphadenectomy and survival

- Single center, retrospective, 1969 – 1990
- 649 patients pelvic node sampling
  - 212 multiple site sampling (mean # 11)
  - 205 limited site sampling (mean # 4)
  - 208 no node sampling
- Multiple site sampling: 8% node (+)
- Limited node sampling: 4% node (+)
- Multiple site vs. no sampling → better survival ( $P < 0.001$ )

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- Multiple site vs. no sampling → better survival ( $P < 0.001$ )
- ***Management surgeon dependent***      ***major bias !!!!***

# Lymphadenectomy and survival

- Retrospective, single center, 1973-2002
- 1656 pts; 619 clinical stage I had lymphadenectomy,  
→509 no gross extrauterine disease
- median no of nodes: 15 (11 pelvic, 3 aortic)
- 5% pelvic; 3% aortic node metastases
- 5-yr OS 83%
- pelvic N+: OS 55%; aortic N+: OS 31%

# Lymphadenectomy and survival

- Overall: no survival difference for  $>11$  vs  $<11$  nodes
- Grade 1-2: no survival difference
- **Grade 3: significantly better OS and PFS if  $> 11$  nodes**

**No protocol, management depends on surgeon (bias) !**

## NCI data

- Retrospective, 14% of US population
- 9185 stage I
- 2821 st I lymph node sampling
- median no of nodes: 7 (1-40)
- 5-yr relative survival stage I: 0.98 vs 0.96 (ns)
- grade 1 or grade 2: no difference
- **stage I, grade 3: 5-yr relative survival 0.89 vs 0.81, (p=0.01)**

# Conclusion from retrospective studies

- Overall influence of nodal staging on survival in patients with early stage EC is small.
- Possible influence in high risk (grade 3) tumors  
(Level 3/4 evidence)

# Disadvantages of nodal staging

- More operative complications
- Increased cost / time
- You (gynecologic oncologist) have to be there



# Morbidity of lymphadenectomy

- Depends upon extend of the staging procedure
- Longer operation time:  $\pm$  30 minutes
- Complete staging: morbidity 18% -19%

5%–7% mild

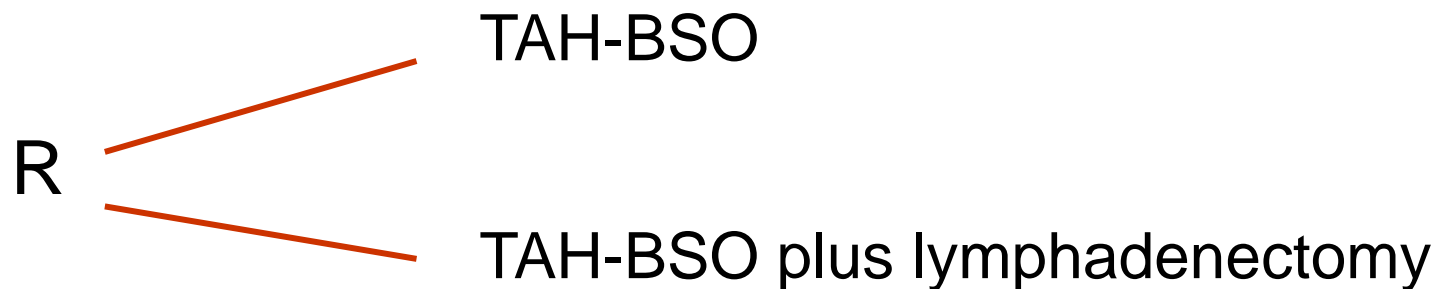
8% moderate

4%–5% severe

**Morrow 1991, Mohan 1998, Fanning 1996, Cragun 2005**

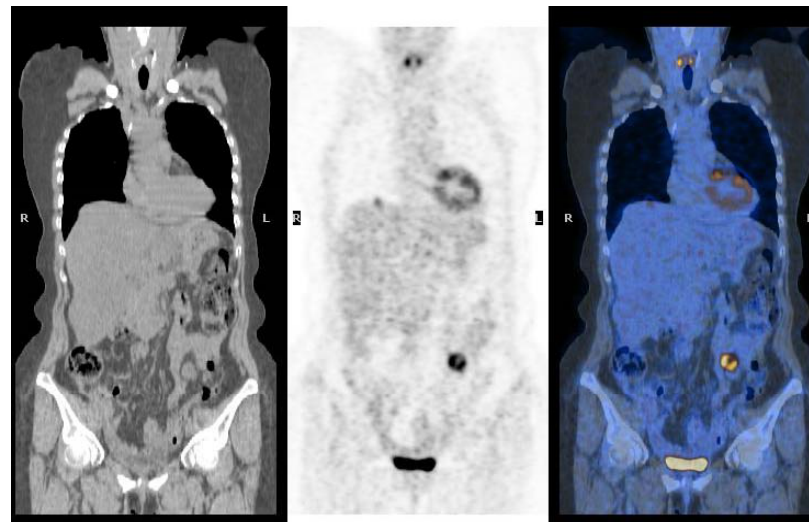
# Randomized trial: ASTEC trial

*Clinical stage I: n = 1408*



- 9% N+, no minimum number of nodes
- 30% RT (both arms)
  - » *no survival or DFS advantage*
  - » *no benefit if >10 or >15 nodes*
  - » *more toxicity (8% lymphedema)*

# Can advanced imaging techniques help us ?



# Validity of FDG-PET in the pre-operative evaluation of Endometrial Cancer

- Sensitivity 69.2%, PPV 42.9%
- Lymphnode metastasis < 1 cm not detected by PET

**No advantage of FDG-PET !**

# Current protocol at UMC St Radboud in Nijmegen

- No nodes in most patients with stage I EC
- Adjuvant radiation treatment following PORTEC

Grade 3

Stage IC (2 out of 3)

Age > 60

**Good evidence**

- Full pelvic and paraaortic node dissection in patients with grade 3 tumors and/or deep invasion (IC)

**Poor evidence!**

# We need a study !!

- Full pelvic and paraaortic lymphadenectomy in high risk stage I EC
- Randomised international study
- N = ?

*Better stratification for type of RT*

*Possible survival advantage*

*Candidates for studies on systemic treatment*



# Stage IC, grade 3 endometrial cancer

*Comparison with PORTEC RT arm*

	PORTEC RT arm	Stage IC, grade 3
Locoregional relapse (5 yr)	1% - 3%	14%
Distant metastases (5 yr)	3% - 8%	31%
Overall survival	83% - 85%	58%