The role of PET-FDG for predicting regional response after CT-RT for HNSCC with advanced regional disease

Protocol submitted to the GETTEC-GORTEC

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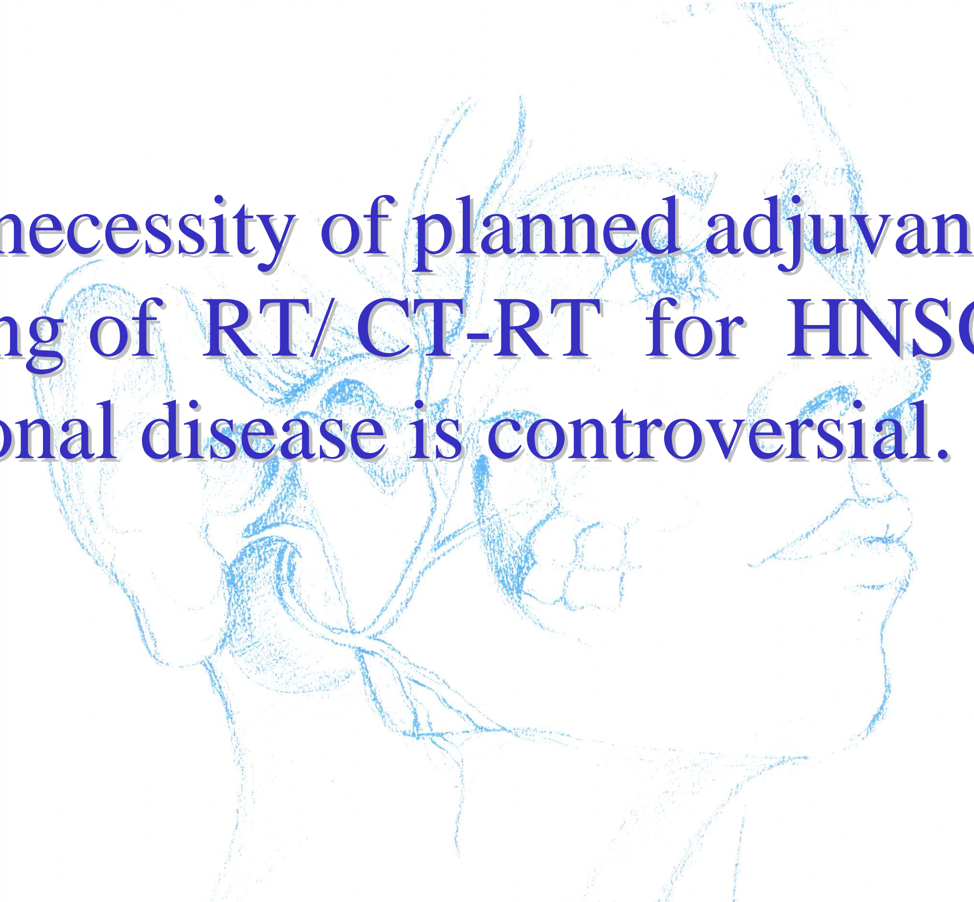
Background



The necessity of planned adjuvant Neck Dissection in the setting of RT/ CT-RT for HNSCC with advanced regional disease is controversial.

Planned ND for HNSCC with advanced regional disease

Pro

- ND after RT improves regional control and disease-free survival.
- Salvage in the event of neck recurrence is unlikely to succeed.

Planned ND for HNSCC with advanced regional disease

Cons

- Probability of isolated neck recurrence following CCR very low.
- Many useless NDs.
- No randomized trial.

Neck Dissection in N2-N3 patients with complete response after CT-RT

3 ways to improve the utility of treatment

- **PET**: to improve the discrimination of clinical assessment.
- **Chemoradiation**: to improve the efficacy of treatment.
- **Selective neck dissection** rather than comprehensive radical neck dissection, to decrease the morbidity.

Is FDG PET as a tool to better predict the necessity for neck dissection ?

Yao M et al . IJROB, 2005, Iowa City

n: 53 N2, N3 70 heminecks

CT + PET median 15 w

ND if residual LN and PET+.

ND or observation if residual LN and PET -.

21 res LN + PET- 4ND (res LN>3cm): pCR 4/4, 17 observed

7 res LN + PET+ 6ND, 1FNA (-) pPR: 3/7

42 res LN - PET- observed

Follow up med 26 m: no regional failure

Specificity	94%	neg predict value	100%
Sensitivity	100%	pos predict value	43%

Is FDG PET as a tool to better predict the necessity for neck dissection ?

Porceddu SV et al. Head Neck 2005   Melbourne

n: 39 stage III-IV, N+, median follow up: 34m

CR primary, residual LN, >8 w post RT.

PET : 8-12 w (80%) , median 12w post RT

PET- : 32   - ND: 5,   pN- 5/5

- no ND: 27, LR failure 1 (neck + primary)

Neg predictive value: 97%

PET+:   7   ND:7,   pN- 2/7 (non viable cells)

Pos predictive value: 71%

Neck Dissection in N2-N3 after CT-RT

Is FDG PET as a tool to better predict the necessity for neck dissection ?

Rogers JW et al . IJROB, 2004 Winston Salem

n: 12 PET 4 w post RT

Sensitivity 45%	neg predict value 14%
Specificity 100%	pos predict value 100%

Mc Collum et al . Head Neck, 2004 Boston

n: 24 PET 4-12 w post CT, CT-RT

Sensitivity 67%	neg predict value 73%
Specificity 53%	pos predict value 46%

Neck Dissection in N2-N3 after CT-RT

Is FDG PET as a tool to better predict the necessity for neck dissection ?

Standardization!!

- Timing of FDG-PET after radiation.
- Treatment outcome % of CCR, CT-RT vs RT alone.
- Timing of neck dissection.
- Quality of PET imaging.

Proposal for a prospective registration study

Aim:

to determine the correlation between FDG-PET findings and pathologic results of post CT-RT neck dissection specimens in case of neck dissection or regional control in case of abstention of surgery in the neck.

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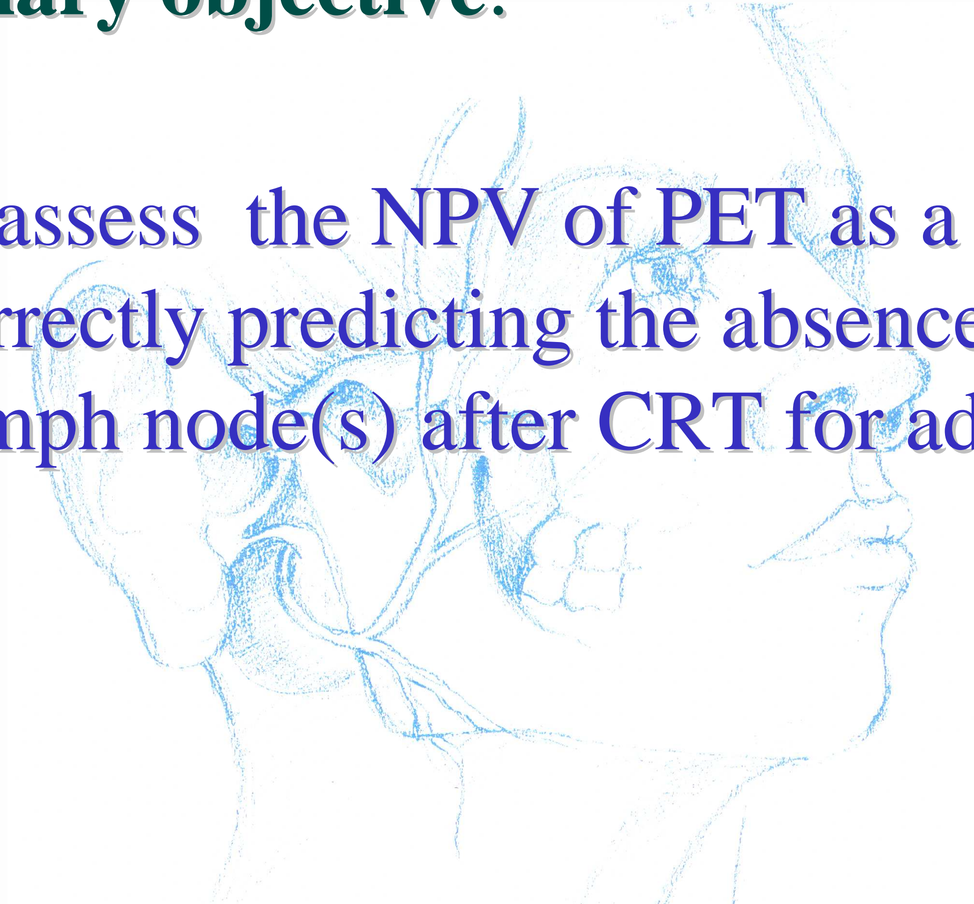
Objectives

Primary objective:



to assess the NPV of PET as a single examination in correctly predicting the absence of remaining invaded lymph node(s) after CRT for advanced HNSCC

Objectives

Secondary objectives:

- Evaluation of the suitability of a wait and see approach without ND in patients considered as complete responders (based on phys ex, CT/MR and PET). The suitability will be estimated using the NPV of the overall assessment of a complete response.

- Evaluation of the ability of PET to correctly predict remaining pathologically invaded lymph nodes (PPV) after CRT in patients with a post CRT positive PET (and who will undergo at least ND)

End Points

End Points:

Regional control, locoregional control, local control, DFS, OS, CT/MR findings ,

PET findings (pre and post treatment),

Types of neck dissection

Complications of neck dissection.

Patient population

Patients eligibility:

- HNSCC oral cavity, oropharynx, hypopharynx,larynx
- Suitable for at least post CRT neck dissection
  T1-T4 N1, N2a, N2b, N2c, N3, M0.
- Scheduled for an organ preservation protocol: concomitant CRT (induction chemo allowed, providing followed by concomitant CRT).

Patient population

Patients eligibility:

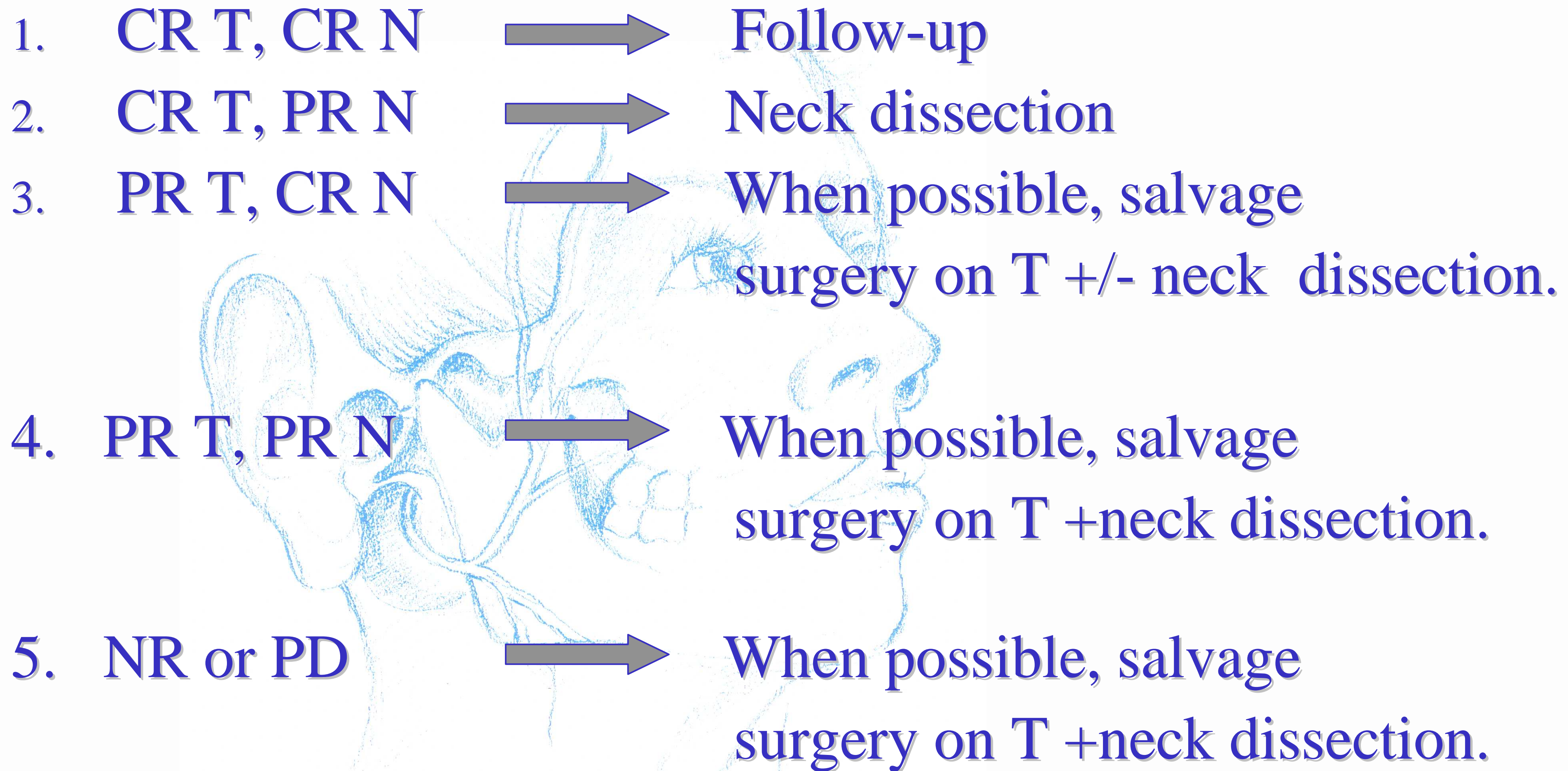
- Patients should be able to undergo neck dissection .
- No previous head & neck cancer treatment.
- No other current malignancy.

Clinical and imaging evaluation

Assessment

- before treatment : clinical examination, CT/MR, PET.
- 10-12 weeks after the end of treatment : clinical examination, CT/MR, PET.

Assessment post CT-RT



1. CR T, CR N → Follow-up
2. CR T, PR N → Neck dissection
3. PR T, CR N → When possible, salvage surgery on T +/- neck dissection.

4. PR T, PR N → When possible, salvage surgery on T +neck dissection.

5. NR or PD → When possible, salvage surgery on T +neck dissection.

FDG-PET

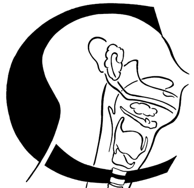
Method (1)

- Biopsy proven non previously treated HNSCC
  T1-T4 N1-N3
- 2 FDG-PET for each patient
  - before therapy
  - 10– 12 weeks after the end of chemoradiation
- Neck dissection in any suspicion of residual regional disease
- Follow up in complete locoregional response

FDG-PET

Method (2)

Same timing : fixed interval between injection of FDG and scanning for each FDG-PET in a given patient to ensure SUV measurement reproducibility (and comparison)



FDG-PET

Method (3)

- Patient positionning (contention masks : idem for radiation)
- Data acquisition
  - Head & neck region covered with 2 or 3 bed positions
  - 10 min emission scan per bed → ↑ image quality
  - Rotating source or CT
- Image interpretation
  - with all the anatomical imaging data available (CT, MRI)
  - Image co-registration and fusion to be performed for each scan (either by software fusion or by PET-CT acquisition)
- Tracer uptake measured by maximal SUV

  → SUV max at base line, at 10– 12 w. after the end of treatment

  → DELTAs will be calculated

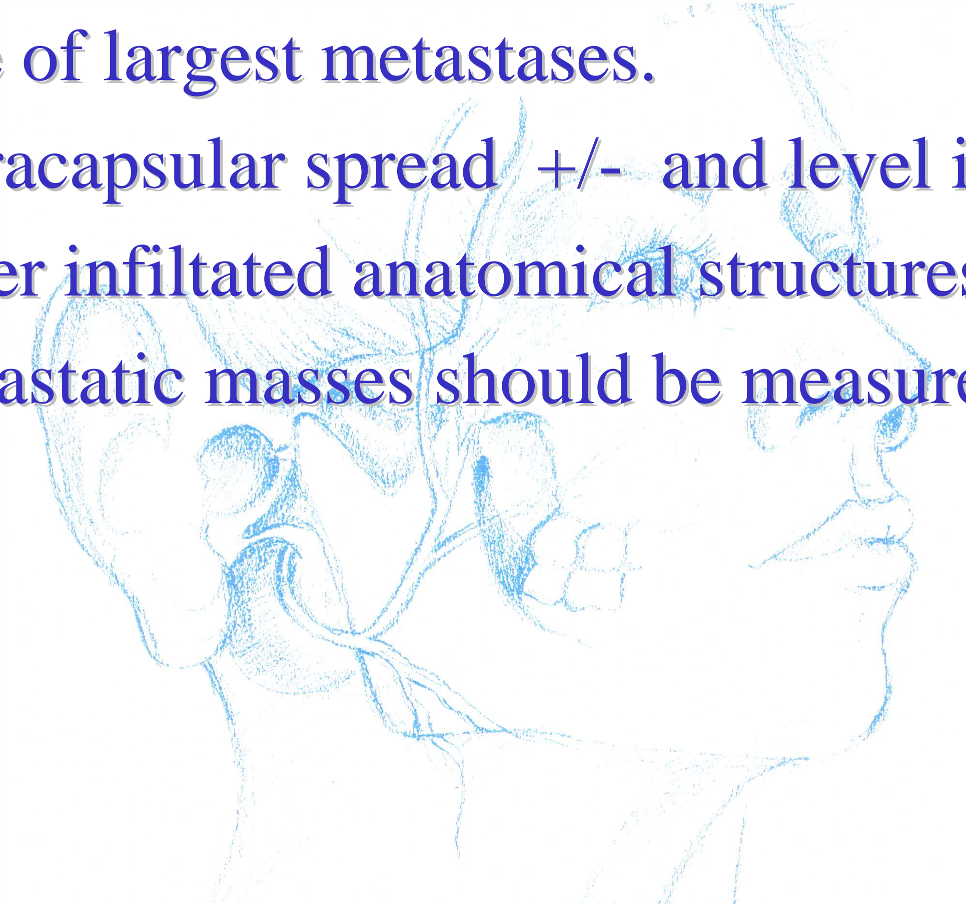
Pathology

Selection of blocks for histology- neck dissection post CRT

- Identify anatomical structures (salivary gland, IJV, SCM…).
- Include small LN as a whole, with a small rim of adipose tissue.
- Large LNs should be sectionned.
- **Include also all fibrous nodules > 3mm.**
- 1H&E slide per LN is enough.
- **The average nb of LNs is usually lower than in a previously untreated RND because of lymphocyte depletion due to RT.**
- Sample all other anatomical structure involved.

Pathology

- For each level, total nb of LNs and nb of metastases.
- Size of largest metastases.
- Extracapsular spread +/- and level involved.
- Other infiltated anatomical structures.
- Metastatic masses should be measured and localized.



Pathology

- **Response to previous treatment:**

  - keratins debris and anucleated squamous cells are non-viable and correspond to a sterilized metastasis. Report as such.

  - if nucleated mature squamous cells persist, do a Ki67 staining ; if negative, cells are probably non-viable and LN is sterilized by therapy. Report as such.

  - if persistence of immature atypical squamous cells, consider as positive and report as such.

- Other features of unknown prognostic significance: micrometastases (<3mm), other LN diseases,…

Sample size evaluation

NPV < 90% not acceptable

NPV ⩾ 95% acceptable

Power statistical test : 90% (one-sided significance level of 5%)

- ➡ 247 patients with PET-
- ➡ assuming 65% of PET-,

  total sample size= **380 patients**

Pending questions

- Optimal timing of post treatment PET. 12w
- Standardization of PET?
- Pathologic analysis of the neck dissection specimens.
- Types of neck dissection: RND,MRND, SND.