Prognostic value of pre-treatment 18FDG-PET in operable breast cancer

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Introduction

Positron emission tomography (PET) is an imaging technique that produces a three-dimensional image of functional processes in the living body. The system detects pairs of gamma-rays emitted indirectly by positron-emitting radionuclide, which is introduced into the body on a biologically active molecule (radiopharmaceutical). From the emitted gamma-rays three-dimensional images of tracer concentration within the body are reconstructed with the aid of powerful computers. In modern PET-scanners scanners, imaging is accomplished with CT that is acquired during the same imaging session, with the patient positioned identically, on the same machine.

The biologically active molecule most frequently chosen for PET imaging in oncology is ^{18}F-Fluoro-deoxyglucose (FDG), a glucose analog. Non-invasive assessment of the glucose metabolism in oncology is of major importance since most cancer cells, on contrast to what normal cells do, predominantly produce energy through increased glycolysis, even in aerobic conditions. This shift in tumor cell glucose metabolism can be demonstrated and quantified by FDG-PET. Today FDG-PET/CT is considered a key imaging tool in a wide variety of oncologic conditions for (re)-staging, monitoring response to treatment as well as for radiotherapy planning.

In case of breast cancer current guidelines acknowledge the use of FDG-PET/CT in patients with clinically suspected of metastasis or recurrence disease [1,2]. The potential of FDG-PET in operable breast cancer however is still debated. Several authors recently showed that pre-operative FDG-PET is a highly significant predictor of outcome in breast cancer [3-12]. The issue deserves close attention, for FDG-PET

should be reconsidered in the initial staging of breast cancer if indeed pre-operative FDG-PET is confirmed as an independent prognostic factor, otherwise not.

Primary objective:

Evaluate the prognostic value of FDG-PET for survival in breast cancer.

Secondary objectives:

- Evaluate the clinical-pathological factors that might be associated with patterns of FDG uptake.
- Check if there are changes of breast cancer management over time, compare the characteristics and outcomes between patients diagnosed 2002-2008 and patients diagnosed 2009-2015.
- Explore whether there are interactions, subgroups of patients in whom FDG-PET might be more important.
- Examine the prognostic role of the regional axillary lymph node-to-primary tumor of maximum standard uptake value (SUVmax) ratio (LN/T SUV ratio) [13-16].

Expected impact of the study

1. Evaluate the long term prognostic value of FDG PET in patients with up to 13 years follow-up.
2. Validate FDG PET in a more recently diagnosed cohort of patients.
3. Identify subgroups of patients in whom FDG PET might be more important: impact on better use of diagnostic resources.
4. Establish hypotheses for the design of FDG PET trials in breast cancer.

Materials, methods

Study type:

Retrospective, non-interventional, single center.

Key words:

Breast cancer, ^{18}F-FDG, PET, PET-CT, survival analysis, prognostic factors.

Number of patients:

1. Considering the primary objective, assuming disease free survival (DFS) at 3 years of 60% in case of PET loco-regional positive status (increased regional uptake), versus 80% DFS at 3 years in case of PET negative status (no increased regional uptake), at significance level of 0. 5, power of 0.80, one sided proportions test, groups of equal size, the total number needed is 128 patients.
2. Taking into account that a subset of patients were previously analyzed (cohort 2002-2008) and that a subgroup comparison between cohorts is

intended, using Bonferroni adjustment of significance level to 0.025, the number needed is 162 patients.

3. Among the secondary objectives, we would like to give precedence to explore the innovative concept of LN/T SUV ratio. Adjusting the significance level to 0.017, the total number needed is 182 patients. On average 15 newly diagnosed breast cancer patients received a PET. We expect that 210 cases might be retrieved from 2002 to 2015.

Selection of patients:

Inclusion criteria:

- Patients treated at the UZ Brussel
- Diagnosed in the period 2002-2015
- Primary breast cancer
- Histologically confirmed
- Operable
- Pre-treatment FDG-PET or PET/CT

Exclusion:

- Previous history of cancer
- Primary sarcoma of the breast
- Palliative surgery for symptom control
- No histopathological confirmation of cancer
- Noninvasive carcinoma
- Metastatic disease demonstrated by imaging modes other than FDG-PET

Data to be collected:

Clinical-pathological characteristics:

- Age at diagnosis
- Gender
- Presentation (screening/symptomatic)
- Lab markers
- Source material of initial pathology (cytological/biopsy/excision)
- Histological tumor type
- Pathological grade
- Hormone receptor status
- Her2/neu status
- Lymphovascular invasion
- Breast inflammation
- Breast skin invasion
- Tumor laterality
- Tumor location
- Clinical tumor size
- Pathological tumor size
- Number of examined axillary lymph nodes
- Number of involved axillary lymph nodes
- Neoadjuvant therapy
- Type of surgery
- Adjuvant chemotherapy

- Adjuvant hormone therapy
- Adjuvant radiation therapy

FDG-PET characteristics:

- Type of exam (PET only/ PET-CT)
- PET positivity (visual pathologically increased uptake): breast, axillary-supraclavicular region, internal mammary nodes, distant metastatic.
- Standard uptake value (SUV) based on regions of interests:
    - SUVmax global (whole body).
    - SUVmax within breast, right and left.
    - SUVmax axillary-supraclavicular region, right and left.
    - SUVmax internal mammary nodes.

Outcomes:

- Local (in-breast) recurrence
- Regional (axillary, supraclavicular, internal mammary nodes) recurrence
- New primary tumor (breast/non-breast)
- Censor status at last follow-up (alive/died)
- Disease status at last follow-up (NED, no evidence of disease/WD, with cancer)
- Cause of death

Dates:

- Date of first histological diagnosis
- Date of first pre-treatment PET/PET-CT
- Date of most recent PET/PET-CT preceding surgery (in case of neoadjuvant therapy).
- Date of surgery
- Date of first recurrence
- Date of last follow-up.

Anonymization of the data

Investigator will allocate unique study number to patients.
Lock the study's master list in a password protected file.
Delete all identification information (name, medical file number) in the file retained for analyses.

Statistical analyses

- Descriptive statistics of clinical- pathological characteristics and patterns of PET uptake.
- Relationship between the characteristics and the patterns of PET uptake.
- Disease-free survival (DFS) analyses: event defined as any local-regional or distant recurrence, new primary tumor, or death from any cause.
- Overall survival (OS) analyses: event defined as death from any cause.
- Explorative analyses: multivariate Cox regression analyses of DFS and OS. Evaluate the prognostic value of patterns of PET positivity using the Akaike information criterion (AIC) and using indexes of the proportion of variation explained by covariates.

- Handling of missing data: if missing in <10% of the cases, impute using multivariate imputation by chained equations [17]. If missing in 10% or more, consider separate analyses.
- **Addressing limitations of the study:**
  - Selection bias, patients who receive pre-treatment FDG PET/PET-CT likely might have more advanced disease than the general population of patients: estimate how they differ from previous UZ Brussel analyses [18-20].
  - Non-blinded retrospective data collection: independent verification of data by co-investigator.
  - Missing data inherent to the study: effort will be made at the time of patient's data abstraction to ascertain from the medical record whether missing data corresponds to usual clinical practice (e.g. patients receiving follow-up in other hospitals typically have missing info), or corresponds to patient's characteristics (e.g. poor clinical condition).
  - Small number of cases for multivariate analyses: restrict inferences.
  - Multiple comparisons: restrict inferences.

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