Attenuation-Corrected vs. Nonattenuation-Corrected 2-Deoxy-2-[F-18]fluoro-D-glucose-Positron Emission Tomography in Oncology, A Systematic Review

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Abstract
Purpose: To perform a systematic review and meta-analysis to determine the diagnostic accuracy of attenuation-corrected (AC) vs. nonattenuation-corrected (NAC) 2-deoxy-2-[F-18]fluoro-D-glucose-positron emission tomography (FDG-PET) in oncological patients.
Procedures: Following a comprehensive search of the literature, two reviewers independently assessed the methodological quality of eligible studies. The diagnostic value of AC was studied through its sensitivity/specificity compared to histology, and by comparing the relative lesion detection rate reported with NAC-PET vs. AC, for full-ring and dual-head coincidence PET (FR- and DH-PET, respectively).
Results: Twelve studies were included. For FR-PET, the pooled sensitivity/specificity on a patient basis was 64/97% for AC and 62/99% for NAC, respectively. Pooled lesion detection with NAC vs. AC was 98% [95% confidence interval (95% CI): 96–99%, n=1,012 lesions] for FR-PET, and 88% (95% CI:81–94%, n=288 lesions) for DH-PET.
Conclusions: Findings suggest similar sensitivity/specificity and lesion detection for NAC vs. AC FR-PET and significantly higher lesion detection for NAC vs. AC DH-PET.
Key words: Deoxyglucose (MeSH), Tomography, X-ray computed (MeSH), Tomography, emission-computed (MeSH), Neoplasms (MeSH), Human (MeSH), Systematic review (MeSH), Attenuation correction, Positron emission tomography

Introduction
The attenuation of photons originating from the subject before they are detected by the camera is a generic limitation of nuclear medicine imaging. This attenuation can lead to image distortion and impairs adequate quantification. Attenuation correction has been commonly employed in 2-deoxy-2-[F-18]fluoro-D-glucose (FDG) imaging in an attempt to correct for these effects. With positron emission tomography (PET) scanners, this is accomplished by transmission scanning using a radionuclide source, such as germanium-68 or cesium-137, and with PET/computed tomography (CT) using CT. With respect to
visual interpretation of the images, the added value of attenuation correction has been controversial. Whereas attenuation correction provides a more realistic image of FDG distribution, its application significantly increases acquisition times on standard full-ring (FR) PET scanners. In addition, the performance of attenuation correction can introduce noise and even artifact. Paradoxically, even if the nuclear medicine community sees attenuation correction, or the lack of it, as a potential effect-modifier of test accuracy, its impact is rarely accounted for in systematic reviews on the diagnostic accuracy of PET. As a result, the impact of attenuation correction on lesion detectability and interpretation of PET for oncological purposes is not well established. With PET/CT scanning, it is customary to evaluate either modality (primarily to account for artifacts), but one needs to know how to deal with discrepancies.

The objective of this systematic review and meta-analysis was to determine the diagnostic accuracy of nonattenuation-corrected (NAC) and attenuation-corrected (AC) FDG-PET in oncological patients. We studied the effects of attenuation correction for both FR-PET and dual-head coincidence PET (DH-PET), and as a function of different body locations (head/neck, chest, abdomen/pelvis).

Materials and Methods

Literature Search

A computer-aided literature search was performed in both Medline and Embase databases without time range or language restrictions, applying controlled vocabulary (MeSH and EMTREE keywords, respectively) as well as free text words. The search date was February 10, 2006. The search strategy (Appendix) included terms for PET with FDG, modified from Mijnhout et al. [1] as well as search terms identifying both radionuclide and X-ray transmission, emission, attenuation correction, and oncological studies in humans. In addition, the reference lists of the eligible articles were reviewed to ensure that relevant articles had not been missed.

Study Selection

From the list of retrieved articles, articles were initially evaluated for eligibility on the basis of title and abstract by two independent reviewers (UJ, PR). If there was uncertainty as to whether an article was eligible for inclusion, the entire article was reviewed. Inclusion criteria were (1) clinical studies evaluating FDG imaging with and without attenuation correction in oncology patients; (2) study population of at least ten patients; (3) sufficient detail to reconstruct a 2×2 contingency table expressing FDG imaging results by disease status, or sufficient detail to reconstruct relative lesion detection measurement of AC vs. NAC imaging; and (4) studies utilizing FR-PET and/or DH-PET. We excluded abstracts, editorials, and reviews, although the latter two categories were used for cross-referencing.

Methodological Quality Assessment

The methodological quality of each article was independently assessed by each reviewer in terms of internal and external validity (Table 1), based on the Cochrane Methods Group in Screening and Diagnostic Tests, modified for our area of interest [2]. Internal validity items focus on whether a valid reference test was used and whether this reference test was uniformly and independently applied and interpreted as well the type of study design. The external validity items evaluate the applicability of the results in terms of the type of patient population and spectrum, demographic information, the inclusion/exclusion criteria, the knowledge of previous test/clinical information that could influence interpretation, and the index test characteristics. Items were scored as positive, negative, or unclear.

Data Extraction and Quantitative Analysis

In addition to methodological quality assessment, data related to the type of camera, the FDG dose, the time interval between injection and imaging, the transmission and emission acquisition protocols, the reconstruction protocol, and the interpretation protocol were independently

| Test | Criteria |
|------|----------|
| A. Internal study validity | Histology, AC FR or DH coincidence PET |
| A1. Valid reference test | Assessment of reference test independent of index test(s) results |
| A2. Blind measurement of reference test(s) without knowledge of index test | Choice of patients assessed by reference test independent of index test result |
| A3. Avoidance of verification bias | Mentioned in publication |
| A4. Index test(s) interpreted independently of all clinical information | Mentioned in publication |
| A5. Prospective study | Localization of disease described (selected or general) |
| B. External study validity | Age and sex given |
| B1. Spectrum of diseases | Mentioned in publication |
| B2. Demographic information | Mentioned in publication |
| B3. Inclusion criteria described | Consecutive series of patients |
| B4. Exclusion criteria described | Described technical aspects of index test(s) |
| B5. Avoidance of selection bias | Mentioned in publication |
| B6. Standardized execution of index test(s) | |
| C. Reproducibility described | |

Table 1. Methodological assessment of individual diagnostic studies: criteria
extracted from each study by each reviewer. For studies where it was possible, a contingency \(2 \times 2\) table was constructed. Disagreements were solved by consensus.

For studies using an independent gold standard (histopathology), we determined the sensitivity and specificity of the index tests using the number of true positive, false positive, true negative, and false negative results from the \(2 \times 2\) contingency table. Furthermore, we calculated the "relative lesion detection," defined as the percentage of lesions scoring equally positive or negative with NAC vs. AC images. We performed a subgroup analysis for different locations of lesions and analyzed sensitivity, specificity, or relative lesion detection of NAC vs. AC for lesion location in the head and neck region, the chest, and the abdominopelvic region. In cases of discrepancy of relative lesion detection between NAC and AC, we extracted data to analyze whether this was related to lesion size and/or intensity.

The statistical diagnostic heterogeneity of the sensitivity and specificity per index test across studies was tested by the chi-square test. In case of statistical heterogeneity of DH- or FR-FDG-PET imaging, a random effect model for pooling was used, whereas in case of statistical homogeneity, a fixed-effect model was used. Sensitivity, specificity, and relative lesion detection were pooled independently, all pooled estimates are presented with 95% confidence intervals (95% CI). The logit transformed sensitivity, specificity, relative lesion detection, and corresponding 95% CI of the index tests were compared using \(z\)-test statistics. A \(p\) value of less than 0.05 was considered significant.

All statistical analyses were performed with the SPSS 11.0.01 program for Windows (version 11.0.1., SPSS, Chicago, IL, USA).

### Results

The search strategy yielded 2,202 references, 1,477 in Medline and 725 in Embase on February 10, 2006. Of the Embase references, 370 were also included in Medline, leaving a total of 1,832 unduplicated references. On the basis of title and abstract alone, 1,806 references were excluded. After review of the full text of the remaining 26 articles, an additional 11 studies [3–12] proved to be ineligible because they did not perform a direct comparison of the yield of NAC vs. AC images in oncological patients. One study [13] was excluded because it was published in abstract form only. Another study [14] was excluded because it was published in Japanese and was not readily translatable. Finally, the study of Hustinx et al. [15], who evaluated the effect of attenuation correction in abdominal tumors for a sodium iodide crystal (NaI) PET scanner, was excluded because no \(2 \times 2\) contingency tables could be constructed. Eventually, we included 12 studies for review [16–27].

A summary of the methodological quality assessment results can be found in Table 2. Methodological quality was scored as negative when quality items were unclear or absent in the original article. In a minority (4/12=33%) of studies, histology served as the reference test. However, nine of the 12 studies provided a direct comparison of AC and NAC PET. In three studies, blind measurement of reference test was performed without knowledge of index test. All but one study avoided verification bias. In four studies, the index test(s) was evaluated independently of all clinical information. All studies provided information about the spectrum of diseases being evaluated and standardized the execution of the index test(s). Almost all studies (11/12=92%) described the demographics of the study population and inclusion criteria. However, only one study mentioned specific exclusion criteria. Six studies were prospective. Only two of the 12 studies specifically mentioned including consecutive patients, and only three studies specifically described the reproducibility of their results.

### Meta-Analysis

Three FR-PET studies were eligible for pooling of sensitivity on a patient basis [22, 24, 25]. The pooled sensitivities for AC and NAC FR-PET were 64% (95% CI 52–74%) and 62% (95% CI 51–73%), respectively (\(n=182\) patients). Two FR-PET studies provided data that allowed pooled analysis of specificity [22, 24]. Weber et al. [25] could not be

| Study      | Year | A1 | A2 | A3 | A4 | A5 | B1 | B2 | B3 | B4 | B5 | B6 | C |
|------------|------|----|----|----|----|----|----|----|----|----|----|----|---|
| Bleckmann  | 1999 | +  | +  | +  | +  | +  | -  | -  | +  | -  | -  | +  | - |
| Chan       | 2001 | +  | -  | +  | +  | -  | -  | +  | +  | +  | +  | +  | - |
| Delbeke    | 2001 | +  | -  | +  | +  | +  | +  | +  | +  | +  | +  | +  | - |
| Even-Sapir | 2004 | +  | -  | +  | +  | +  | +  | +  | +  | +  | +  | +  | - |
| Kotzerke   | 1999 | +  | -  | +  | +  | +  | +  | +  | +  | +  | +  | +  | - |
| Lonneux    | 1999 | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | - |
| Nakamoto   | 2002 | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | - |
| Reinhardt  | 2005 | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | - |
| Schauwecker| 2003 | +  | -  | -  | -  | +  | +  | +  | +  | +  | +  | +  | - |
| Weber      | 1999 | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | - |
| Zimny      | 1999 | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | - |
| Zimny      | 2003 | +  | -  | +  | +  | +  | +  | +  | +  | +  | +  | +  | - |
included as there were no patients without disease. The pooled specificities for AC and NAC FR-PET were 97% (95% CI 92–99%) and 99% (95% CI 95–100%), respectively (n=155 patients). For DH-PET, only one study provided data on sensitivity and specificity [27].

Relative lesion detection for NAC vs. AC PET was pooled for 11 studies, which are demonstrated in Fig. 1. Lesion detection of NAC FR-PET vs. AC FR-PET was 98% (95% CI: 96–99%) for n=1,012 lesions (pooling of n=7 studies); 79% of which were classified FDG positive at AC FR-PET. Lesion detection of NAC DH-PET vs. AC DH-PET was 88% (95% CI: 81–94%) for n=288 lesions (pooling of n=4 studies); 74% of which were classified as FDG-positive at AC DH-PET.

In addition, we evaluated the relative lesion detection depending on body location (head/neck, chest, abdomen/pelvis) in the four FR-PET [20, 21, 23, 26] and in the three DH-PET studies that provided sufficiently detailed information [17, 18, 26]. The relative sensitivity and specificity based on body location could not be calculated due to an insufficient number of studies. For FR-PET, we found similar relative lesion detection for the three body locations: 95% for head/neck (95% CI 84–98%, n=61 lesions), 97% for the chest (95% CI 94–99%, n=396 lesions), and 97% for the abdomen/pelvis (95% CI 93–0.99%, n=205 lesions). For DH-PET, relative detection rates for NAC were not significantly different for the various body sites: 78% in the abdomen/pelvis (95% CI 65–88%; 53 lesions), 84% in the chest (95% CI 74–91%; 136 lesions), and 90% in the head/neck area (95% CI 73–97%; 38 lesions). However, in chest (p=0.000089) and abdomen/pelvis (p=0.0037), the relative detection rates with NAC (vs. AC) for DH-PET were significantly lower than those obtained with FR-PET.

A comprehensive analysis of the potential association of relative detection and lesion size and/or intensity, for lesions with discrepant AC and NAC results, was not possible due to a lack of detailed information. We summarized the results in Table 3: findings of Bleckmann et al. and Reinhardt et al. [16, 23] suggest that AC and NAC discrepancies may relate to (intrapulmonary) lesion size with more discrepancies occurring with smaller lesions at the subcentimeter level (an average of 3% of lesions were correctly detected with NAC and not with AC). The single discrepant lesion in the study of Weber et al. concerned a ≥1-cm lesion in the mediastinum [25]. However, the discrepant lesions in the studies of Nakamoto et al., Schauwecker et al., and Delbeke et al. included both small- and moderate-sized lesions (in relation to lesions included each study) [18, 22, 24]. In the study of Schauwecker et al., the discrepant lesions demonstrated SUVmax values rang-
Weber et al. FR-PET 1 0.8 cm Not given

Conversely, with DH-PET, AC images demonstrated a higher detection rate as opposed to NAC images, which is surprising given that AC images are significantly enhanced uptake on AC images and equivocal uptake on NAC images.

Discussion

The cumulated evidence summarized in this systematic review of oncological FDG imaging studies suggests that the accuracy of attenuation and nonattenuation corrected FR-PET are similar. However, with DH coincidence imaging NAC images detect 12% less lesions than AC images, without prominent differences between body areas.

Although in the nuclear medicine field attenuation correction is generally seen as an important issue, it is surprising to find that several large systematic reviews did not thoroughly consider this as a potential effect-modifier. Gould et al. performed systematic reviews on FDG PET in pulmonary lesions [28] and mediastinal lymph node staging in non-small cell lung cancer [29]: in the former review, the item was not mentioned, and in the latter, attenuation correction was an item of study quality, but no analysis of potential impact was performed.

The choice of the reference test is obviously relevant in studies on test accuracy. In oncology, histopathology is the typical endpoint. Of the 12 eligible studies, four used histology as an independent gold standard. Meta-analysis of sensitivity and specificity was only possible for FR-PET, and we found no significant difference for either measure. We chose to use the AC detection rate as an alternative reference test, which defines the relative lesion detection of NAC vs. AC images. This choice theoretically biases in favor of AC: Bleckmann et al. and Reinhardt et al. [16, 23] reported an average of 3% more true positive lesions with NAC FR-PET. However, we expect that the resulting error is small because, in the comparison with histopathology, false positive rates were quite low for either modality. Despite this theoretical negative bias towards NAC, similar lesion detection rates were observed with both AC and NAC for FR-PET. Hence, attenuation correction may not contribute to the detection of malignancy using FR-PET. Conversely, with DH-PET, AC images demonstrated a significantly higher detection rate as opposed to NAC images, which is surprising given that AC images are usually significantly noisier than NAC images. We postulate that this may be secondary to differences in reconstruction/filtering algorithms.

In addition, there are limitations associated with performing a meta-analysis and data pooling, such as the homogeneity of the data and the quality of the published studies. Homogeneous data have higher statistical strength than heterogeneous data. The data in our study were heterogeneous so that we used a random effect model for pooling. In addition, the statistical strength of the meta-analysis is limited by the quality of the published studies included in it. As mentioned earlier and summarized in Table 2, the studies had several quality limitations. Finally, meta-analyses are limited by publication bias, which biases towards the publication of favorable results or popular subjects.

We were surprised by the limited number of good comparative studies evaluating the value of attenuation correction. It appears that attenuation correction has been accepted as the standard of practice without sound scientific evidence to support it.

The introduction of PET/CT machines has made the time constraints associated with transmission scanning less of an issue. However, PET/CT is not a panacea; X-ray transmission scanning has its own problems and numerous PET/CT publications have demonstrated artifact that can be introduced with X-ray transmission scanning [5, 30–45]. Furthermore, in the study of Reinhardt et al. [23], a significantly improved visibility was demonstrated for 41% of lung metastases with NAC images as opposed to CT-AC images. This higher visibility for NAC images was even more pronounced for lesions smaller than 1 cm. These findings underline that even as PET/CT use becomes more widespread, evaluation of both NAC and AC images should remain an integral part of image interpretation, and not just to recognize image artifacts. At the same time, NAC vs. AC discrepancies at PET/CT offer an obvious opportunity for further investigation.

Conclusions

In this meta-analysis, we found no significant difference in sensitivity, specificity, or relative lesion detectability between AC and NAC FR FDG PET. However, attenuation...
correction improved lesion detection for DH coincidence imaging.

Appendix

Detailed search strategy

(“x-ray” OR x-ray OR cine-et OR “Tomography, X-Ray Computed” [mesh] OR transmission OR attenuat* OR nonattenuat* OR ac[tw] OR nac [tw] OR nonac OR germanium OR ge[tw] OR gallium OR ga[tw] OR cesium OR cs[tw]) AND (oncolog* OR cancer* OR neoplas* OR neoplasms[mesh] OR tumor* OR tumor OR tumors OR carcinoma* OR melanom* OR lymphom* OR malignant*) AND (Deoxyglucose[mesh] OR Deoxyglu-
ose[tw] OR Deoxyglucose[tw] OR Deoxyglucose[tw] OR deoxy-glucose [tw] OR Deoxy-d-glucose[tw] OR Deoxy-d-glucose[tw] OR Fluordeoxyglu-
cose[tw] OR Fluordeoxyglucose[tw] OR Fluordeoxyglucose[tw] OR fluorodeoxyglucose[tw] OR fluorodeoxy-glu-
cose[tw] OR Fluoro-d-glucose[tw] OR Fluoro-d-glucose[tw] OR Fluorodeoxyglucose[tw] OR Fluorodeoxyglucose[tw] OR fluoro-deoxyglucose[tw] OR fluoro-
d-glucose[tw] OR fluoro-d-glucose[tw] OR fluorodeoxyglucose[tw] OR fluorodeoxy-glucose[tw] OR fluorodeoxy-glu-
cose[tw] OR Fluoro-d-glucose[tw] OR Fluoro-d-glucose[tw] OR Fludeoxyglu-
cose[tw] OR Fluordeoxyglucose[tw] OR fluorodeoxyglucose[tw] OR 18fluorodeoxyglucose[tw] OR 18fluorodeoxyglucose OR 18fluorode-
yo-glucose[tw] OR 18fluorodeoxyglucose OR 18fluorodeoxy-
glucose[tw] OR 18fluorodeoxyglucose OR 18fluorodeoxy-
glucose[tw] OR fisg*[tw] OR fisg[tw] OR fisg-[tw] OR fisg-[tw] OR fisg-[tw] OR fluorodeoxyglucose[tw] OR 2deoxy-d-glucose[tw] OR ((fluor[tw] OR fluoro[tw] OR 18fluor[tw] OR 18fluoro[tw]) AND glucose[tw]) AND (pet[tw] OR pet* OR petcan* OR “Tomography, emission-computed” [mesh] OR (position[tw] AND emission[tw] AND tomograph* [tw]) OR (emission[tw] AND computed[tw] AND tomog-
ramh*[tw])) NOT (animal [mesh] NOT human[mesh])

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