Cancer is one of the leading causes of death worldwide. Accurate diagnosis, staging and restaging are essential for the optimal therapeutic management of cancer patients. Positron emission tomography (PET) with 2-deoxy-2-[fluorine-18]fluoro-D-glucose (18F-FDG), an analogue of glucose, provides valuable functional information based on the increased glucose uptake and glycolysis of cancer cells and depicts metabolic abnormalities before morphological alterations occur. 18F-FDG PET/CT acquires PET and CT data in the same imaging session and allows accurate anatomical localization of the lesions detected on the 18F-FDG PET scan. Following its introduction, integrated PET/CT rapidly gained clinical acceptance, and in the last decade it has become an important imaging tool in routine clinical oncology.

There is evidence that 18F-FDG PET/CT is particularly useful for detecting recurrence, especially in asymptomatic patients with rising tumor marker levels and those with negative or equivocal conventional imaging findings. Yet there are some limitations and areas of uncertainty, mainly regarding the lack of specificity of 18F-FDG uptake and the variable avidity of some cancers for this tracer. This article reviews the main applications, advantages and limitations of 18F-FDG PET/CT in oncology.

METHODS
A search was performed to identify mainly all published randomized controlled trials and systematic reviews in the English language literature. An additional search was performed to identify relevant unpublished systematic reviews. These publications comprised both retrospective and prospective studies of variable methodological quality. The consequences of false-positive and false-negative test results when evaluating the clinical usefulness of tests, as well as the impact of 18F-FDG PET/CT on the management of cancer patients, were also reviewed.

Breast Cancer
18F-FDG PET/CT has no role in the diagnosis of primary breast cancer as its ability to detect small and/or
noninvasive carcinomas is poor, with an overall sensitivity of only 68% for tumors of size <2 cm.\textsuperscript{1,2} For axillary nodal staging, \textsuperscript{18}F-FDG PET/CT has variable sensitivity (79%-94%) and specificity (86%-92%),\textsuperscript{3,4} and therefore the predictive accuracy is insufficient to recommend this modality for routine use.\textsuperscript{5}

The most important current clinical applications of \textsuperscript{18}F-FDG PET/CT in breast cancer patients are for the detection and evaluation of recurrent or metastatic disease (Figure 2) and for monitoring response to therapy.\textsuperscript{6} In a patient-based analysis, it was shown that \textsuperscript{18}F-FDG PET/CT has a high overall sensitivity, specificity and accuracy for the detection of locoregional recurrence (89%, 84% and 87%, respectively) and distant metastases (100%, 97% and 98%, respectively) (Table 2) and is also more sensitive than the serum tumor marker CA 15-3 in detecting relapsed disease.\textsuperscript{7}

Detection of a decrease in the standardized uptake value (SUV) to a level below 55% of the baseline study is a powerful tool in monitoring histopathological response to chemotherapy for locally advanced breast cancers. Using this criterion, \textsuperscript{18}F-FDG PET/CT was found to have a sensitivity of 100%, a specificity of 85% and an accuracy of 88% in identifying responders after the first cycle, while corresponding values after the second cycle were 83%, 94% and 91%.\textsuperscript{8} After a single pulse of chemotherapy, \textsuperscript{18}F-FDG PET was able to predict complete pathological response with a sensitivity of 90% and a specificity of 74%.\textsuperscript{9} The reported overall survival in \textsuperscript{18}F-FDG PET/CT nonresponders is 8.8 months, compared with 19.2 months in responders.\textsuperscript{10} In the case of bone metastases, the responding bony lesion may become more sclerotic on the CT component of \textsuperscript{18}F-FDG PET/CT while its \textsuperscript{18}F-FDG activity reduces, which is a sign of bone healing.

Colorectal Cancer
In colorectal cancer, \textsuperscript{18}F-FDG PET/CT plays a pivotal role in the detection of recurrent disease, the assessment of residual post-therapy masses, the localization of recurrence in patients with an unexplained rise in serum carcinoembryonic antigen (CEA) and the staging of patients before surgical resection of local recurrence and distant metastatic disease.\textsuperscript{11} For the detection of intra-abdominal but extrhepatic colorectal recurrence, the sensitivity of \textsuperscript{18}F-FDG PET/CT is 88%; the specificity, 94%; and accuracy, 92%. For extra-abdominal and/or hepatic recurrence, the sensitivity is 95%; specificity, 100%; and accuracy, 99%. The overall reported average sensitivity, specificity and accuracy for detecting recurrent disease
**Table 2.** Sensitivity, specificity and accuracy of 18F-FDG PET/CT in different tumor types and settings.

|                      | Sensitivity (%) | Specificity (%) | Accuracy (%) | References |
|----------------------|-----------------|-----------------|--------------|------------|
| **Breast cancer**    |                 |                 |              |            |
| Locoregional recurrence | 89              | 84              | 87           | 7          |
| Distant metastasis   | 100             | 97              | 98           | 7          |
| Early response assessment | 83-100         | 85-94           | 88-91        | 8          |
| **Colorectal cancer**|                 |                 |              |            |
| Recurrence           | 89              | 92              | 90           | 12         |
| Intra-abdominal/extrahepatic recurrence | 88          | 94              | 92           | 12         |
| Extra-abdominal and/or hepatic recurrence | 95           | 100             | 99           | 12         |
| **Oesophageal cancer**|                 |                 |              |            |
| Metastases (M-staging) | 43-78           | 93-99           | 62-86        | 30-34      |
| Recurrence (locoregional and distant) | 94           | 82              | 87           | 42         |
| **Head and neck cancer** |             |                 |              |            |
| Initial staging (nodal) | 94              | 84              | 90           | 46, 47     |
| Restaging/recurrence | 88              | 78              | 86           | 55         |
| **Lung cancer**      |                 |                 |              |            |
| Solitary pulmonary nodule | 81-100         | 63-100          | 90-92        | 90-92      |
| Mediastinal staging (N2/N3) | 67-92         | 82-99           | 84-96        | 65-68      |
| Recurrence           | 93-100          | 89-92           | 86-88        | 89         |
| Response to treatment (≥80% threshold) | 90           | 100             | 96           | 95         |
| **Lymphoma**         |                 |                 |              |            |
| Initial staging and restaging (HL) | 86              | 96              | 95           | 95         |
| Nodal involvement in HL or high-grade NHL | 94            | 100             | 96           | 96         |
| Organ involvement in HL or high-grade NHL | 88            | 100             | 96           | 96         |

The residual pelvic soft tissue abnormalities frequently seen in the tumor bed region after therapy usually complicate the detection of local recurrence by the conventional imaging techniques. Abnormal 18F-FDG activity in a residual pelvic soft tissue lesion after 6 months from the completion of radiotherapy most likely represents tumor recurrence, and accuracy and positive predictive value (PPV) are even higher after 12 months. Elevated CEA levels are seen in two-thirds of patients with recurrent colorectal cancer. The use of 18F-FDG PET/CT for preoperative radiotherapy planning in rectal cancer significantly alters both the gross tumor volume and the clinical target volume, with a mean increase in size of 25% and 4%, respectively. The use of 18F-FDG PET/CT is emerging as a potentially valuable technique in radiotherapy planning, as well as in the prediction and evaluation of response to therapy. The use of 18F-FDG PET/CT for preoperative radiotherapy planning in rectal cancer significantly alters both the gross tumor volume and the clinical target volume, with a mean increase in size of 25% and 4%, respectively. The use of 18F-FDG PET/CT is emerging as a potentially valuable technique in radiotherapy planning, as well as in the prediction and evaluation of response to therapy. The use of 18F-FDG PET/CT for preoperative radiotherapy planning in rectal cancer significantly alters both the gross tumor volume and the clinical target volume, with a mean increase in size of 25% and 4%, respectively.

**Esophageal Cancer**

Endoscopic ultrasound (EUS) provides more accu-
rate and cost-effective T-staging and N-staging than $^{18}$F-FDG PET/CT and conventional CT\textsuperscript{26-28} and remains the standard for local tumor evaluation.\textsuperscript{29} The most important role of $^{18}$F-FDG PET/CT in the initial staging of esophageal cancer lies in M-staging (Figure 4) through its ability to identify unexpected metastases (i.e., metastases not visible on conventional imaging), which are present in up to 30% of the patients.\textsuperscript{30} $^{18}$F-FDG PET/CT has better sensitivity, specificity and accuracy (43%-78%, 93%-99% and 62%-86%, respectively) than CT and EUS for the detection of distant metastases (Table 2).\textsuperscript{30-34} In M-staging, the addition of $^{18}$F-FDG PET/CT results in up-staging of 15% to 20% and down-staging of 5% to 7% of the patients.\textsuperscript{34,35} In addition, synchronous primary tumors are identified in 5.5% of patients, of which 75% are not identified by conventional imaging.\textsuperscript{36}

Assessment of tumor response to neoadjuvant therapy by $^{18}$F-FDG PET/CT has been found to be an important prognostic factor,\textsuperscript{37} with a reported diagnostic accuracy of 85%; this is similar to the diagnostic accuracy of EUS (86%) and significantly higher than that of conventional CT (54%).\textsuperscript{38}

In patients with squamous cell carcinoma of the esophagus and some inoperable cases, $^{18}$F-FDG PET/CT plays an important role in radiotherapy planning,\textsuperscript{39-41} with a reported modification of gross tumor volume in 56% of the patients and alteration of the planning treatment volume in 53%.\textsuperscript{41}$^{18}$F-FDG PET is a highly sensitive tool for the detection of regional and distant recurrences, with a reported sensitivity, specificity and accuracy of 94%, 82% and 87%, respectively, in comparison to 81%, 82% and 81% for conventional imaging. Furthermore, $^{18}$F-FDG PET depicted recurrences in 12% of the patients with negative or equivocal findings on conventional imaging.\textsuperscript{42}

**Head and Neck Cancer**

$^{18}$F-FDG PET/CT has an impact on the assessment of both newly diagnosed and previously treated patients with head and neck cancer.\textsuperscript{43} $^{18}$F-FDG PET/CT alters the initial clinical staging and TNM category of the tumor in 14% to 57% of the patients when compared with...
CT-based evaluation alone, and has an accuracy of approximately 90% compared with 86% for conventional CT. The reported sensitivity and specificity of standard 18F-FDG PET/CT for the detection of lymph node metastases in a per-patient analysis were 94% and 84%, respectively (Table 2), in comparison to 78% and 84% for conventional CT.

18F-FDG PET/CT has been found to identify synchronous primaries in 8.1%, distant metastases in 15.4% and the site of an unknown primary in 73% of the patients with head and neck cancer. In addition, it alters the initial management in 18% to 37% of the patients. The impact of 18F-FDG PET/CT on radiotherapy planning is especially important; planning is changed in 29% of the patients, with an alteration in the gross tumor volume in 57% of the patients. It has been reported that the gross tumor volume is statistically significantly larger with 18F-FDG PET/CT-based assessment than with CT-based assessment. There is still a high risk of locoregional recurrence (18%-31%) and distant metastasis (20%-25%) despite aggressive treatment. The sensitivity, specificity and accuracy of 18F-FDG PET/CT in restaging patients with head and neck cancer are 88%, 78% and 86%, respectively.

Postoperative, but pre-radiotherapy, 18F-FDG PET/CT evaluation within a median of 4 weeks after surgery has been found to alter the course of management in 15% of the patients. In addition, it has a higher accuracy than conventional CT when used at 4 to 8 weeks following the end of chemoradiotherapy, with an even higher sensitivity and specificity after 8 weeks.

**Lung Cancer**

Correct initial staging of non-small cell lung cancer (NSCLC) is important in distinguishing operable patients from those who are inoperable, but can benefit from neoadjuvant treatment. The American College of Chest Physicians guidelines recommend 18F-FDG PET for noninvasive staging owing to the low sensitivity and specificity of the commonly used conventional CT in mediastinal nodal staging. 18F-FDG PET/CT is a more accurate method and is the emerging standard test for preoperative diagnosis and staging of NSCLC; it changes the course of management in up to 52% of cases and has a major role in reducing the number of futile thoracotomies.

Diagnostic accuracy and sensitivity of 18F-FDG PET/CT staging of lung cancer in terms of operability have recently been reported to be 79% and 64%, respectively, in comparison to 60% and 32% for conventional staging. The initial reported sensitivity and specificity for 18F-FDG PET in mediastinal nodal assessment are 67% to 92% and 82% to 99%, respectively (Table 2), in comparison to 25% to 71% and 66% to 98% for CT alone. Overall, the correct stage is assessed by 18F-FDG PET in 85% to 96% of the cases as compared with 58% to 59% by conventional CT alone, and 18F-FDG PET has a negative predictive value (NPV) of 97% (CT, 87%). Sensitivity, specificity and accuracy of 18F-FDG PET/CT for the depiction of malignant nodes are 85%, 84% and 84%, respectively, in comparison to 70%, 69% and 69% for CT alone.

The high NPV of 18F-FDG PET/CT (up to 97%) for mediastinal disease has led to the recommendation to omit mediastinoscopy in patients with negative mediastinal 18F-FDG PET/CT. However, special attention should be paid to central tumors, which have a high incidence of occult N2 disease. If 18F-FDG PET/CT is positive, then mediastinoscopy is necessary to exclude a false-positive result. 18F-FDG PET/CT detects unexpected extrathoracic metastases (Figure 5) in 11% to 15% of asymptomatic patients, avoiding futile surgical intervention.

18F-FDG PET/CT is useful for radiation therapy planning since it provides more accurate initial staging, allowing omission of elective radiation of clinically uninvolved nodal stations. In addition, its CT data may be used for radiation therapy planning if properly acquired. This modality can be successfully applied to...
patients with limited-disease small cell lung cancer for whom the treatment is concurrent chemoradiotherapy, with a reported 24% change in the treatment field.\textsuperscript{79}

Post-treatment fibrosis and scarring are common, and \textsuperscript{18}F-FDG PET/CT is more accurate than conventional CT in detecting residual and recurrent disease, which allows more reliable treatment planning decisions.\textsuperscript{80-83} In addition, conventional CT alone has been shown to be suboptimal in mediastinal restaging after treatment.\textsuperscript{84,85} \textsuperscript{18}F-FDG PET has sensitivity of 93% to 100% and a specificity of 89% to 92% for detecting recurrent NSCLC.\textsuperscript{86-88} Patients with residual \textsuperscript{18}F-FDG uptake after treatment have a poor prognosis when compared to those without residual \textsuperscript{18}F-FDG uptake, taking into consideration the expected post-therapeutic inflammatory changes to avoid false-positive interpretation.\textsuperscript{84}

Reduction in the baseline maximum SUV on \textsuperscript{18}F-FDG PET is predictive of a complete pathologic response with a sensitivity of 90%, a specificity of 100% and an accuracy of 96%, irrespective of the cell type or neoadjuvant treatment.\textsuperscript{89} Indeterminate solitary pulmonary nodules (SPNs) remain a clinical dilemma. \textsuperscript{18}F-FDG PET/CT currently should be reserved for cases where CT-guided fine-needle biopsy either is technically difficult or has been non-diagnostic.\textsuperscript{90} Compared with CT scan, \textsuperscript{18}F-FDG PET has similar sensitivity but better specificity in depicting malignancy in SPNs, the reported values ranging from 81% to 100% and from 63% to 100%, respectively.\textsuperscript{90-92}

**Lymphoma**

\textsuperscript{18}F-FDG PET/CT is now an established standard in the initial staging, monitoring of response to therapy and restaging after treatment of patients with Hodgkin lymphoma (HL) and high-grade non-Hodgkin lymphoma (NHL).\textsuperscript{93} The clinical utility of \textsuperscript{18}F-FDG PET/CT depends on the pathological subtype but not necessarily on the tumor grade.\textsuperscript{94} \textsuperscript{18}F-FDG PET/CT shows a sensitivity of 86% and a specificity of 96%, in comparison to 81% and 41% with conventional CT alone, in disease assessment (presence or absence) of HL during both initial staging and restaging.\textsuperscript{95} In patients with HL or high-grade NHL, the sensitivity and specificity of \textsuperscript{18}F-FDG PET/CT for lymph node involvement are 94% and 100%, respectively, while for organ involvement they are 88% and 100% (Table 2).\textsuperscript{96}

False-negative scans are noted in MALT (mucosal-associated lymphoid tissue) lymphomas, which are not highly metabolically active.\textsuperscript{97} Aggressive (high-grade) NHL typically shows more intense \textsuperscript{18}F-FDG activity in comparison to lower-grade NHL, although there is significant overlap between them.\textsuperscript{96} Detection of an FDG-avid lesion in a documented low-grade NHL should raise the suspicion of transformation to a higher-grade lymphoma.\textsuperscript{97,98} Infectious and/or inflammatory diseases are known causes of false-positive \textsuperscript{18}F-FDG PET/CT scans, and the possibility of their presence should be entertained at interpretation.\textsuperscript{99-102} Residual post-therapy masses are seen in up to 85% of the cases of HL and up to 40% of the cases of NHL.\textsuperscript{103,104} Early interim \textsuperscript{18}F-FDG PET/CT results (after two to four cycles) correlate well with event-free survival in HL (Figure 6)\textsuperscript{105-107} and high-grade NHL.\textsuperscript{108,109} In high-grade NHL, the event-free survival at 2 years and 5 years has been reported to be 82% and 88.8%, respectively, for negative interim PET patients in compassion to 43% and 16.2%, respectively, for positive interim PET patients.\textsuperscript{108,109} In another study, the 2-year event-free survival in HL patients with negative interim \textsuperscript{18}F-FDG PET was 95% in comparison to 12.8% in those with positive interim \textsuperscript{18}F-FDG PET.\textsuperscript{107}

**Thyroid Cancer**

More than 90% of thyroid cancers are differentiated, comprising papillary and follicular carcinoma.\textsuperscript{110} In de-differentiated thyroid cancer, recurrent or metastatic tumor cells may lose the expression of sodium iodide symporter and have a decreased ability to concentrate...
radioiodine.\textsuperscript{111} A multicenter trial showed that the sensitivity of \textsuperscript{18}F-FDG PET is 85\% in patients with raised thyroglobulin and negative 131I whole-body scans.\textsuperscript{112} In this subgroup of patients, \textsuperscript{18}F-FDG PET/CT alters clinical management in 23\% to 51\% of the patients.\textsuperscript{113-118}

**Urological Cancer**

**Renal cell carcinoma**

\textsuperscript{18}F-FDG PET/CT has limited sensitivity in the evaluation of metastatic renal cell carcinoma (RCC), particularly for small metastatic lesions. However, a positive \textsuperscript{18}F-FDG PET/CT scan should be considered strongly suspicious for local recurrence or metastasis because of the high specificity and PPV of this test. A combined test (PET/contrast-enhanced CT) may be necessary if important management decisions are to be based on the test result.\textsuperscript{119}

**Prostate cancer**

Currently there is no established role for \textsuperscript{18}F-FDG PET/CT in the assessment of prostatic cancer, since it has a low accuracy owing to the relatively low metabolic rate of the tumor as well as the interfering adjacent urinary excretion of the tracer. However, other new PET radiotracers such as \textsuperscript{11}C-choline and \textsuperscript{18}F-fluorocholine have shown promising results in the management of prostate cancer.\textsuperscript{119}

**Bladder cancer**

Currently there is no established role for \textsuperscript{18}F-FDG PET/CT in the assessment of bladder cancer, since the high adjacent physiological urinary excretion of the tracer renders the signal-to-noise ratio unfavorable for lesion detection.

**Gynecological Cancers**

**Cervical cancer**

\textsuperscript{18}F-FDG PET/(CT) has a major role in preoperative staging of advanced cervical cancer and restaging after treatment.\textsuperscript{120,121} \textsuperscript{18}F-FDG PET has a sensitivity of 86\%, a specificity of 94\% and an accuracy of 92\% for detection of para-aortic nodal metastases in patients with advanced cervical cancer and negative abdominal CT.\textsuperscript{122} Furthermore, preoperative evaluation with \textsuperscript{18}F-FDG PET influences patient management in 18\% of patients; while in the case of recurrent cervical cancer, \textsuperscript{18}F-FDG PET shows an overall sensitivity of 86\% to 94\% and specificity of 76\% to 100\%.\textsuperscript{123} The 2-year progression-free survival rate is 86\% for patients with a negative post-treatment scan in comparison to 40\% for those with persistent abnormal \textsuperscript{18}F-FDG uptake.\textsuperscript{124}

**Ovarian cancer**

\textsuperscript{18}F-FDG PET/(CT) has a major role in the evaluation of recurrent ovarian cancer when there is an increase in serum CA-125 and inconclusive or negative conventional (CT/MRI) imaging.\textsuperscript{125} The reported sensitivity and PPV of \textsuperscript{18}F-FDG PET/CT for detection of recurrent disease at least 1 cm in size are 83.3\% and 93.8\%, respectively.\textsuperscript{125}

**Cutaneous Melanoma**

There is no role for \textsuperscript{18}F-FDG PET/CT in early cutaneous melanoma (American Joint Committee on Cancer stages I and II).\textsuperscript{126,127} In advanced (AJCC stages III and IV) and recurrent cutaneous melanoma, \textsuperscript{18}F-FDG PET shows 100\% sensitivity for visceral and abdominal nodal metastases and 100\% accuracy for superficial lymph node metastases, but lower sensitivity for pulmonary metastases.\textsuperscript{128} However, the CT component of a combined PET/CT scan would allow better evaluation of pulmonary metastases. The reported rate of synchronous tumor on \textsuperscript{18}F-FDG PET was 4.3\%.\textsuperscript{129} \textsuperscript{18}F-FDG PET results in changes in staging in 12\% to 34\% of the patients\textsuperscript{130,131} and changes in overall management in 8\% to 61\% of the patients.\textsuperscript{132,133}

**Brain Tumors**

Sensitivity and specificity of \textsuperscript{18}F-FDG PET/CT in evaluating low-grade and recurrent tumors and treatment-induced changes are relatively low, mainly owing to the adjacent high physiological brain \textsuperscript{18}F-FDG activity; however, this can be improved significantly by co-registration with magnetic resonance imaging and potentially by delayed imaging. \textsuperscript{18}F-FDG PET/CT is capable of identifying anaplastic transformation of a documented low-grade tumor and has a prognostic value.\textsuperscript{134}

**Pitfalls**

It is extremely important to consider some pitfalls of \textsuperscript{18}F-FDG PET/CT imaging during scan interpretation. The ability to detect tumors depends on various factors, such as their size, metabolic activity, the surrounding background activity and the serum glucose level. False-negative results may be obtained in small lesions (<7 mm), in tumors with a low metabolic rate (e.g., differentiated neuroendocrine tumors, prostate cancer, hepatocellular carcinoma, MALT and mucinous adenocarcinoma), in the presence of interfering cytostatic treatments that may decrease the tumor \textsuperscript{18}F-FDG uptake and when there is suboptimal preparation of patients with glucose intolerance or diabetes (since elevated serum glucose levels result in decreased FDG uptake in tumors owing to competitive inhibition). In addition,
Figure 7. A 62-year-old woman with history of breast cancer. The left column images (MIP and axial PET images) show the normal-intensity images, which could hide metastatic deposits and give a false-negative result due to the physiological high background intensity of the brain. The same images after reducing their intensity on the right column show the metastatic deposits.

Local high physiological FDG activity (as in the brain and the genitourinary tract) can render the signal-to-noise ratio unfavorable for lesion detection (Figure 7), and may give rise to a false-negative result by masking a malignant lesion.

On the other hand, activated macrophages, neutrophils, fibroblasts and granulation tissue show increased $^{18}$F-FDG activity; therefore, infectious/inflammatory processes (e.g., granulomatous diseases, abscesses, active thyroiditis), post-surgical changes (healing surgical wounds, scars, stoma, tube placement) and post-radiation changes (active fibrosis, radiation pneumonitis) may demonstrate increased $^{18}$F-FDG activity and cause a false-positive result.

The Future
As to the evolving role of $^{18}$F-FDG PET/CT and possible future directions for PET/CT, the need to evaluate early response to therapy remains, and there are no good imaging tools at present. Data shows that $^{18}$F-FDG PET/CT predicts not only response to therapy, but also further hard endpoints, such as time to progression. It is likely that more well-designed and large clinical studies on $^{18}$F-FDG PET/CT will expand its approved clinical indications in this context. Currently the majority of PET/CT investigations in oncology use $^{18}$F-FDG (glucose metabolic marker) as a tracer. However, the changing demand to evaluate tumor angiogenesis, tumor hypoxia, tumor cell proliferation and tumor receptors, has led to the development of other specific tracers, which will get greater clinical acceptance with time.
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