

In Vivo Imaging as a Pharmacodynamic Marker

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Abstract

Although numerous anticancer drugs are widely used in the clinic, many questions remain about pharmacokinetics, biodistribution, toxicities, and efficacy. Positron emission tomography (PET) using radiolabeled drugs is a promising method to further understand the clinical behavior of anticancer agents. In addition, it may contribute to better guided treatment planning in individual patients with cancer. Among the available anticancer drugs, considerable experience has been gained with radiolabeling taxanes. At present, two radiolabeled taxanes, paclitaxel and docetaxel, are available as PET tracers. In the present review, data available for the labeled taxanes [¹⁸F]paclitaxel and [¹¹C]docetaxel are discussed and linked to clinical observations following paclitaxel and docetaxel therapy, respectively. In addition, the review discusses the applications and the future of PET using radiolabeled drugs. Experience gained with [¹⁸F]paclitaxel and [¹¹C]docetaxel may be extrapolated to other taxanes and may provide a framework for the development and clinical implementation of other radiolabeled anticancer drugs, even outside the taxane era.

See all articles in this CCR Focus section, "Progress in Pharmacodynamic Endpoints."

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Introduction

Over the past two decades, a number of drugs have obtained a significant position in the treatment armamentarium of various malignancies. Although there is a lot of experience with most anticancer drugs, many questions remain, for example, about pharmacokinetics, biodistribution, toxicities, and efficacy. Positron emission tomography (PET) using radiolabeled anticancer drugs may help to answer at least some of these questions (1), as this technique enables *in vivo* imaging of drug pharmacokinetics and pharmacodynamics. Radiolabeled drugs may be useful to study the pharmacodynamics of anticancer agents, to the extent that we can evaluate whether drug concentrations are sufficient at the tumor site, and not primarily distributed to normal tissue in which toxicity might be expected. In particular, PET may provide insight into factors (e.g., interpatient variability and comedication) that influence drug delivery to tumors and subsequently affect drug efficacy. Among the available anticancer drugs, considerable experience has been gained with radiolabeling of the traditional taxanes. To illustrate the applications and the future of PET using radiolabeled anticancer drugs, this review will discuss the experience with these radiolabeled taxanes.

Taxanes

Originally, taxanes were derived from specific yew trees (2, 3), but nowadays these agents are synthesized artificially (4). Taxanes bind to tubulin and promote the production of stable, but dysfunctional microtubules (5, 6). This interference with microtubule function leads to disrupted mitosis and cell death. To date, four taxanes (paclitaxel, docetaxel, nab-paclitaxel, and cabazitaxel) are available in the clinic. Paclitaxel (7) and docetaxel (8, 9) were first approved for the treatment of patients with cancer in 1992 and 1996, respectively. Nab-paclitaxel (10) and cabazitaxel (11) have been registered more recently in 2005 and 2010, respectively. Taxanes have been approved as single agents and in combination with other agents for the treatment of different types of malignancies in different stages, including breast cancer, ovarian cancer, prostate cancer, Kaposi sarcoma, bladder cancer, non-small cell lung cancer (NSCLC), squamous cell carcinoma (SCC) of the head and neck, esophageal cancer, gastric cancer, and other cancer types (4, 12). In these malignancies, taxanes have shown proven efficacy, including tumor response and improved survival. Nevertheless, treatment failure of taxanes occurs and patients are often subjected to numerous hematologic and nonhematologic toxicities without gaining benefit. At present, two radiolabeled taxanes, paclitaxel and docetaxel, are available as PET tracers (13–17).

Positron Emission Tomography

In clinical practice, PET is an important nuclear imaging technique for diagnosis, staging, and response monitoring of cancer (18). To date, 2-deoxy-2-[¹⁸F]fluoro-D-glucose ([¹⁸F]FDG) is the most widely used PET tracer in oncology. Malignant tumors often show high [¹⁸F]FDG uptake,

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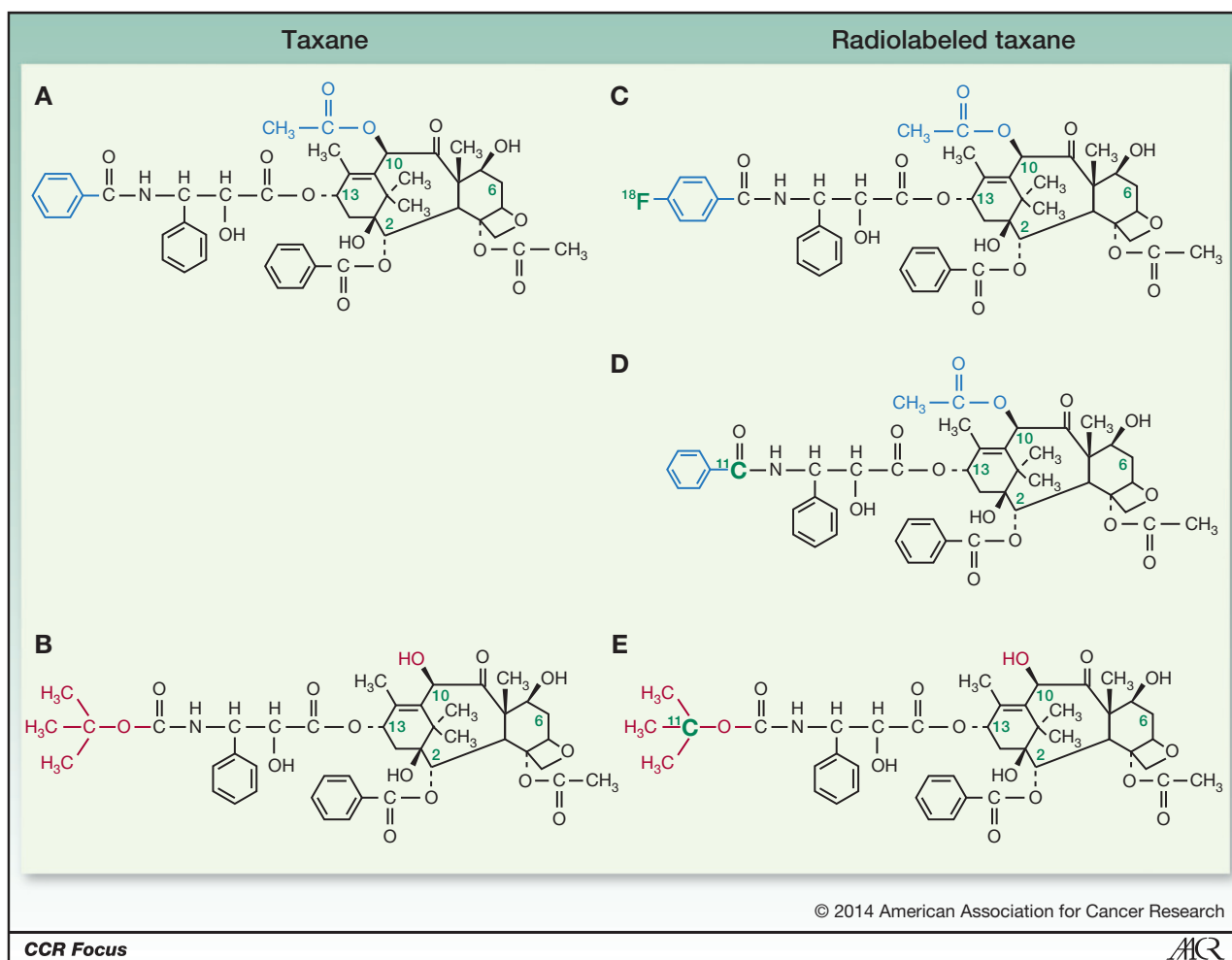


Figure 1. Molecule structures of paclitaxel (A), docetaxel (B), [¹⁸F]paclitaxel (C), [¹¹C]paclitaxel (D), and [¹¹C]docetaxel (E). Blue and red colors indicate differences in molecule structures between paclitaxel and docetaxel. Green color indicates the radionuclide (¹⁸F or ¹¹C) of the radiolabeled taxane.

which is due to enhanced glucose metabolism in many cancer cells (18, 19). Increased [¹⁸F]FDG uptake in tissue, however, is not specific for malignancies and it does not provide information on other more specific biologic characteristics of tumors. Therefore, other PET tracers have been developed. To this end, molecules of interest, for example, anticancer drugs, have been labeled with short-lived positron emitting radionuclides such as oxygen-15 (¹⁵O), carbon-11 (¹¹C), and fluorine-18 (¹⁸F). After intravenous injection of such a tracer, the radionuclide decays and produces high energy gamma rays that are emitted from tissue. Subsequently, these emitted gamma rays can be detected by the PET camera. Thereafter, acquired data are reconstructed, providing three-dimensional (3D) images of the tracer distribution within the body. Anatomical localization of tracer uptake is provided by low-dose computed tomography (CT), which is integrated in state-of-the-art PET-CT scanners (20). As mentioned above, both paclitaxel and docetaxel have been labeled with positron emitters (13–17), there-

by enabling PET studies to monitor pharmacokinetics and pharmacodynamics of these taxanes noninvasively (21).

Radiolabeling of Taxanes

When labeling drugs with positron emitters, the ideal labeling position within the drug molecule needs to be considered. The molecular structure of paclitaxel and docetaxel consists of an eight-member taxane ring, a four-member oxetane ring, and a bulky ester side chain at C-13 that is essential for antitumor activity (Fig. 1A and B). The two taxanes are different in the 10 position on the baccatin ring and in the 3'-position of the lateral chain (22). The chemical formula of paclitaxel is C₄₇H₅₁O₁₄ and its molecular weight is 853.9 g·mol/L, whereas the chemical formula of docetaxel is C₄₃H₅₃NO₁₄ with a molecular weight of 807.9 g·mol/L. Paclitaxel and docetaxel have been labeled with the positron emitters fluorine-18 and carbon-11, having half-lives of 109.8 and 20.4 minutes, respectively (13–17). Both [¹⁸F]paclitaxel

and [^{11}C]paclitaxel have been synthesized, whereas docetaxel has only been labeled with carbon-11, resulting in [^{11}C]docetaxel. In the synthesis of [^{18}F]paclitaxel, the chemical structure is changed by incorporation of fluorine-18 in the molecule (Fig. 1C; ref. 14), thereby potentially changing the clinical behavior of the drug. Conversely, the molecular structures of [^{11}C]paclitaxel (15) and [^{11}C]docetaxel (16, 17) are identical to those of the parent drugs, as a stable carbon atom is replaced by carbon-11 (Fig. 1D and E). Of the three tracers mentioned, [^{18}F]paclitaxel and [^{11}C]docetaxel have been taken further and assessed in preclinical and clinical studies. On the basis of the typical specific activities of these tracers (23, 24), microdoses of approximately 1 to 30 μg are finally injected, which are about 0.001% to 0.01% of the usually administered therapeutic doses. Consequently, no drug-related toxicities are observed after administration of these radiolabeled taxanes (23, 25).

Acquisition and Analysis of PET Data

PET makes it possible to evaluate the distribution of radiolabeled taxanes in normal tissues and tumors noninvasively. For example, whole-body PET scans, which are usually performed in the clinic, enable visualization of the tracer within the whole body. These whole-body scans are static scans and are generated by moving the scanner bed over multiple bed positions. However, whole-body scans are not suitable for absolute quantification, as these scans do not provide data on tracer delivery, blood flow, and specific uptake. For complete characterization of tracer kinetics *in vivo*, dynamic PET scans are required (Fig. 2). A dynamic PET scan is acquired at only one bed position, thereby obtaining detailed kinetics within a selected part of the body. As the field of view of modern PET scanners is approximately 15 to 20 cm, only a relatively small part of the body can be examined. Dynamic scans provide time-activity curves (TAC), which describe the tracer concentrations in tissue over time (Fig. 2B and C). From these TACs, kinetic rate constants of tracer kinetic (compartment) models can be estimated (26). In general, standard single-tissue and two-tissue compartment models are used to describe the distinct behavior of each tracer *in vivo* (Fig. 2D). These models allow for full quantification of tracer kinetics in tissue by incorporating the differential effects of delivery, blood flow, first pass extraction, possible reversible or irreversible binding in tissue, and subsequent washout from tissue (27). For kinetic modeling, a tissue TAC is fitted to the appropriate model equation using the arterial plasma TAC as input function. To this end, an arterial input function can be obtained by either arterial blood sampling (28) or a noninvasive image-derived input function (29), which is less invasive and can be generated from a large arterial blood structure (e.g., the aorta) within the field of view. For appropriate estimation of the kinetic parameters, the input function needs to be finally corrected for changing plasma/blood ratios and the build-up of radiolabeled metabolites during the course of the scan.

Blood kinetics of [^{18}F]Paclitaxel and [^{11}C]Docetaxel

Despite similarity in chemical structures, the metabolism of paclitaxel and docetaxel is distinct. Whereas the metabolism of paclitaxel is known to be species dependent (30), docetaxel metabolism is similar across species. For both drugs, hepatobiliary excretion is the main pathway of elimination and a major fraction of the dose is excreted in feces as parent drug or metabolite. After intravenous injection in humans, both [^{18}F]paclitaxel and [^{11}C]docetaxel are cleared rapidly from blood (23, 25, 31) through the liver and gastrointestinal tract, whereas a minor component is excreted through the kidneys (23, 25). Although it is known that radioactive metabolites can be formed from radiolabeled drugs (32), no radioactive metabolites of [^{18}F]paclitaxel (23) or [^{11}C]docetaxel (25, 31) have been detected in humans. These findings indicate that if radioactive metabolites are produced, none of them enter the bloodstream during the course of the PET scan and, consequently, none are transported to tumors. Nevertheless, radioactive metabolites from [^{18}F]paclitaxel have been detected in monkeys (33). It is conceivable that the amount of radioactive metabolites from [^{18}F]paclitaxel has been too small for detection in humans, as [^{18}F]paclitaxel shows rapid clearance and 85% of the injected dose is still in its parent form for the first 20 minutes after injection in monkeys (33). On the other hand, the species-dependent metabolism of paclitaxel (30) may explain the discrepancy in blood kinetics between humans and monkeys.

Biodistribution of [^{18}F]Paclitaxel and [^{11}C]Docetaxel

Although biodistribution studies are not primarily designed to measure tumor uptake, these studies provide information that may help to explain clinical observations such as efficacy and drug-related toxicities. In addition, data obtained from these studies provide insight in the potential applications of the tracer under investigation. Using whole-body scans, dosimetry and biodistribution of [^{18}F]paclitaxel and [^{11}C]docetaxel have been evaluated in humans (23, 25). Administration of [^{18}F]paclitaxel and [^{11}C]docetaxel was safe in humans with an effective dose of 28.8 and 4.7 $\mu\text{Sv}\cdot\text{MBq}/\text{L}$, respectively. The higher effective dose of [^{18}F]paclitaxel is attributed to the longer half-life of fluorine-18. Successive whole-body PET scans showed that both [^{18}F]paclitaxel and [^{11}C]docetaxel accumulate extensively in the liver and subsequently are excreted into the bile and ultimately into the intestine (Fig. 3; refs. 23, 25). For example, almost 50% of the total injected dose of [^{11}C]docetaxel is taken up by the liver at 1 hour after injection (25). This extensive hepatobiliary accumulation corresponds with observations that liver dysfunction is associated with a reduced clearance of the therapeutic dose, subsequently contributing to a higher risk of severe side effects (34).

In contrast with the liver, biodistribution studies have shown low uptake of [^{18}F]paclitaxel and [^{11}C]docetaxel in

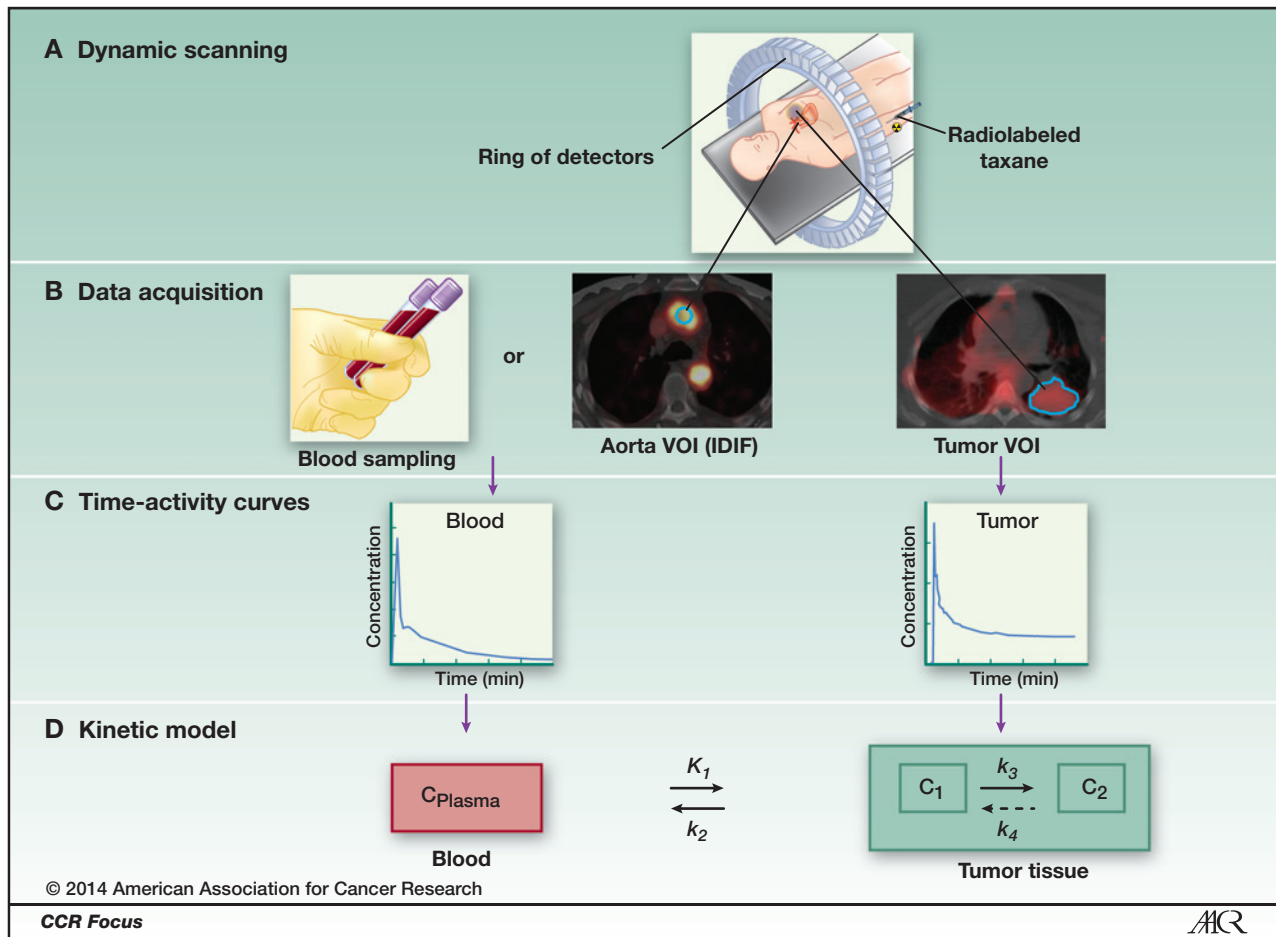


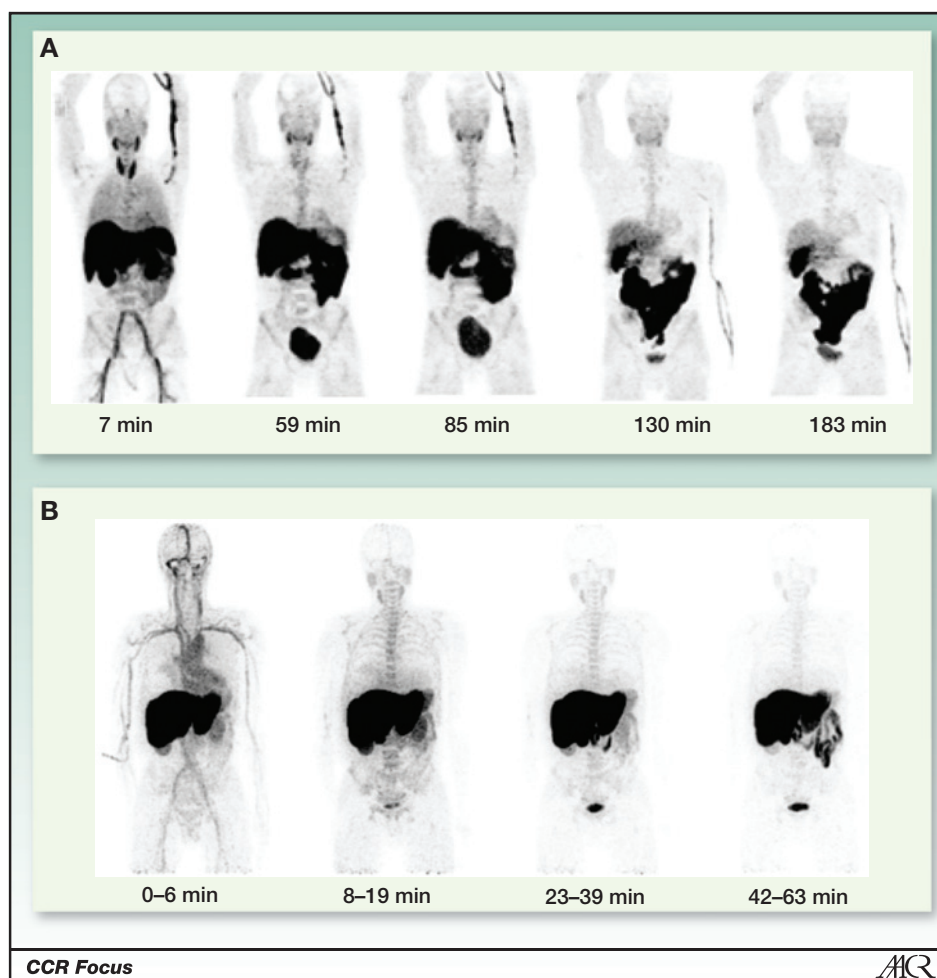
Figure 2. Overview of compartmental modeling of dynamic PET scans using radiolabeled taxanes. A, a patient with lung cancer is intravenously injected with a radiolabeled taxane, simultaneously starting a dynamic PET scan. B, left, concentrations of the tracer in blood can be obtained from arterial blood sampling. Alternatively, an IDIF can be generated from a large arterial blood structure (e.g., the aorta) within the field of view of the dynamic PET scan. Right, tumor VOI is defined on the dynamic PET scan. For the purpose of illustration, PET-CT fusion images from different [¹¹C]docetaxel scans are displayed. C, Left, blood samples or IDIF provide a TAC of blood (right) tumor VOI provides a TAC of tumor tissue. D, TACs of blood and tumor can be entered in the compartment model. In this schematic diagram of a two-tissue compartment model, the concentration (C) in the tumor consists of tracer in compartments 1 (C₁) and 2 (C₂), representing free and bound tracer, respectively. Kinetics of the tracer in tumor tissue are regulated by input from plasma (C_p). Four kinetic rate constants, *k*₁, *k*₂, *k*₃, and *k*₄. *k*₁ are the rate constants describing transport from plasma to tumor; *k*₂ is the rate constant for clearance from tumor to plasma, and *k*₃ and *k*₄ are kinetic rate constants describing exchange between the two tumor compartments. *k*₄ = 0 for the irreversible two-tissue compartment model, which has been applied for kinetic modeling of [¹⁸F]paclitaxel and [¹¹C]docetaxel (23, 31) IDIF, image-derived input function; VOI, volume of interest.

the brain (14, 23, 25, 35). The brain is protected by the blood-brain barrier, which prevents toxins from accumulating in brain tissue. In the blood-brain barrier, the efflux transporter ABCB1 (formerly known as p-glycoprotein or MDR1) is expressed (36, 37). As both docetaxel and paclitaxel are well-characterized substrates of this efflux transporter (38, 39), these drugs essentially cannot penetrate the brain and often show failure in the treatment of tumors and metastases in the brain (40, 41). As a result, several inhibitors of ABCB1, such as cyclosporin A and tariquidar, are under investigation to improve uptake of ABCB1 substrates in the brain (42, 43). Although the effects of a disturbed blood-brain barrier have not been evaluated in the previous PET studies, it is conceivable that [¹⁸F]paclitaxel and [¹¹C]docetaxel may easily penetrate the brain in case of a

disturbed blood-brain barrier (e.g., whole-brain radiation or brain metastases). Remarkably, increased uptake of both [¹⁸F]paclitaxel and [¹¹C]docetaxel has been observed in the pituitary gland (44, 45), which is an endocrine organ that is located in the skull base. This hypophyseal accumulation can be explained by the fact that the posterior pituitary gland is not protected by the blood-brain barrier. Therefore, it is conceivable that other anticancer drugs, including other taxanes, will show similar uptake in the pituitary gland. Although acute side effects on the pituitary gland are not commonly reported for most cytotoxic agents, it is conceivable that chemotherapy may have late effects. For example, the higher risk for pituitary adenomas in breast cancer survivors, previously treated with cyclophosphamide, methotrexate, and 5-fluorouracil (46), may be

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Figure 3. Whole-body PET scans showing comparable biodistribution of [^{18}F]paclitaxel and [^{11}C]docetaxel in humans. Both [^{18}F]paclitaxel and [^{11}C]docetaxel first accumulate in liver, before being excreted into bile and ultimately into intestine. A, five successive [^{18}F]paclitaxel whole-body PET scans in a healthy volunteer (23). This research was originally published in Kurdziel et al. Human dosimetry and preliminary tumor distribution of 18F-fluoropaclitaxel in healthy volunteers and newly diagnosed breast cancer patients using PET/CT. *J Nucl Med* 2011;52:1339-45. © by the Society of Nuclear Medicine and Molecular Imaging, Inc. B, four successive [^{11}C]docetaxel whole-body PET scans in a patient with cancer (25). The shorter half-life of [^{11}C]docetaxel prohibited measurements at 180 minutes. Because of high [^{11}C]docetaxel uptake in the liver, these projections do not show high uptake of [^{11}C]docetaxel in the gallbladder.



explained by drug accumulation in the pituitary gland. Therefore, future studies are needed to investigate (late) effects of chemotherapy on the pituitary gland.

Other tissue accumulation that should be mentioned includes uptake of [^{18}F]paclitaxel and [^{11}C]docetaxel in the vertebral body (45, 47), as well as in the parotid and submandibular glands (47, 48). Increased tracer uptake has been measured in the vertebral body (45, 47), which may clarify the drug-related neutropenia (49) and even the efficacy of docetaxel in patients with hormone refractory metastatic prostate cancer, as 90% of these patients have bone metastases, in particular, in the lumbar level of the spine (50). However, this hypothesis remains to be proven. Furthermore, increased uptake of both tracers was observed in the parotid and submandibular glands (45, 48), suggesting that chemotherapy may contribute to radiotherapy-related xerostomia in patients with locally advanced SCC of the head and neck.

As previously mentioned, biodistribution studies can help to clarify the efficacy of taxanes in specific organs. In addition, the biodistribution of [^{18}F]paclitaxel and [^{11}C]docetaxel reveals background uptake of the tracer in normal organs, thereby identifying tumor types that can be

monitored using PET. High tracer uptake in liver and intestine makes it unlikely that [^{18}F]paclitaxel and [^{11}C]docetaxel can be applied for imaging of the abdominal region. In addition, relatively high tracer uptake in the vertebral body makes it also unlikely that these tracers are useful for imaging bone metastases. Consequently, patients with metastatic prostate cancer are excluded, as these patients frequently present with metastatic sites in paraaortic lymph nodes, pelvic lymph nodes, and spine (50). Although [^{18}F]paclitaxel and [^{11}C]docetaxel seem to be not suitable for imaging of tumors below the diaphragm, low tracer uptake in the thoracic region in humans (23, 25) makes them interesting tracers for tumors located in the thoracic region, including breast cancer and lung cancer.

Delivery of [^{18}F]Paclitaxel and [^{11}C]Docetaxel to Tumors

Because whole-body PET scans do not provide data for absolute quantification of tracer kinetics in tumors, dynamic PET scans have been performed to measure tracer delivery to human tumors (51). Quantitative measurements using Patlak graphical analysis revealed rapid, but rather low

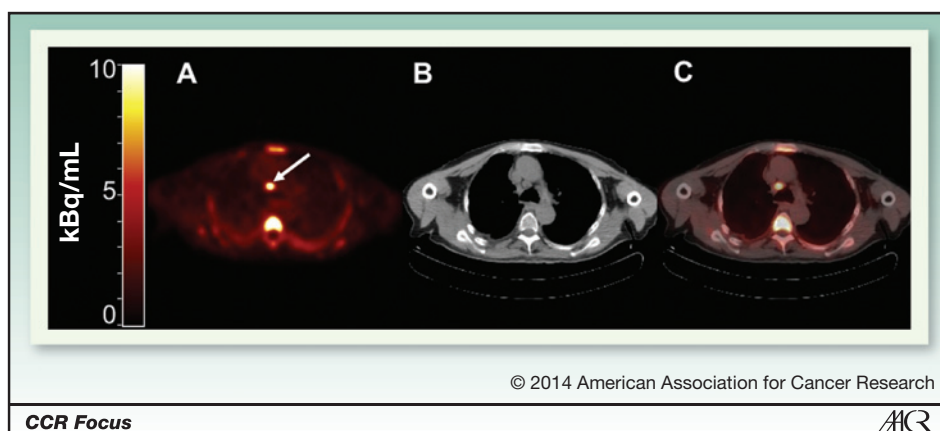


Figure 4. A, summed PET image of [^{11}C]docetaxel uptake from 10 to 60 minutes after injection showing a mediastinal metastasis with increased uptake. B, corresponding CT image. C, PET-CT fusion image reprinted from van der Veldt and colleagues (31).

irreversible uptake of both [^{18}F]paclitaxel (23) and [^{11}C]docetaxel (31) in breast cancer and lung cancer, respectively. This relatively low uptake in tumors is in line with the results obtained from biodistribution studies (23, 25) and may be explained by the rapid clearance of the two tracers from blood (23, 25, 31). For [^{11}C]docetaxel, factors that may affect tumor uptake have been further investigated in patients with lung cancer (Fig. 4; refs. 24, 31). In these studies, accumulation of [^{11}C]docetaxel in tumors was variable and associated with tumor perfusion, but not with tumor size. In addition, patients who were routinely premedicated with dexamethasone (52, 53), which is a potent inducer of the drug efflux transporter ABCB1, showed lower tumor uptake of [^{11}C]docetaxel (31), indicating that comedication may affect drug uptake in tumors. As a microdose is <1% of the therapeutic dose (54) and kinetics of tracer and therapeutic doses may be different (55–59), tumor kinetics of [^{11}C]docetaxel were compared after a regular bolus injection of [^{11}C]docetaxel as well as during an infusion of therapeutic docetaxel (24). It was shown that tumor kinetics of [^{11}C]docetaxel were not significantly affected by therapeutic doses and, therefore, could predict tumor uptake of these therapeutic doses. Furthermore, it was demonstrated that only less than 1% of the total infused dose of docetaxel accumulates in human tumors, indicating the need for strategies to enhance drug delivery to tumors. Finally and most importantly, it was shown that high tumor uptake of [^{11}C]docetaxel is related with improved tumor response in patients with lung cancer (24, 31). Summarizing, these results indicate that [^{11}C]docetaxel PET microdosing studies may predict tumor response to docetaxel therapy and this may hold true also for other radiolabeled taxanes (60).

Effects of Bevacizumab on [^{11}C]Docetaxel Delivery

In clinical practice, taxanes are frequently combined with other anticancer drugs, which may affect taxane delivery to tumors. In this regard, the effect of antiangiogenic drugs is of special interest, as antiangiogenic drugs may transiently

normalize the structurally and functionally abnormal tumor vasculature (61), thereby potentially influencing the delivery and efficacy of taxanes. Therefore, effects of the antiangiogenic drug bevacizumab on tumor uptake of [^{11}C]docetaxel were evaluated in patients with NSCLC (62). Bevacizumab, a monoclonal antibody that targets circulating VEGF, seemed to reduce both perfusion and net influx rate of [^{11}C]docetaxel within 5 hours. These rapid decreases still persisted after 4 days and are in line with the previously mentioned relation between blood flow and [^{11}C]docetaxel delivery in tumors. As no evidence was found for a substantial improvement in drug delivery to tumors after administration of bevacizumab, these findings have clinical implications and indicate that the timing of drug administration may be essential for maximal efficacy (63–65). Here, PET using radiolabeled taxanes may help to optimize drug scheduling of taxane-containing combination therapies.

Future Perspectives

Although numerous anticancer drugs, including taxanes, have been radiolabeled (1), there seems to be a discrepancy between the number of radiolabeled anticancer drugs and the relatively small number of clinical studies. This discrepancy may be due to several potential caveats on the path from development to clinical implementation of these PET tracers, as it can be challenging due to technical, logistical, financial, and patient-related issues. For the development of radiolabeled anticancer drugs, a complex and expensive research infrastructure is required, including a cyclotron, an on-site good manufacturing practice laboratory, a PET/CT scanner, and dedicated computers and software. In addition, these facilities need to be staffed by highly qualified personnel, including cyclotron operators, chemists, radiopharmacists, technologists, physicians, and physicists. As the half-lives of most PET tracers are short, these facilities and personnel need to be located and working in the same building at very close proximity. Finally, clinical implementation may be further hampered by technical problems associated with the characteristics of a specific PET tracer,

such as challenging tracer synthesis, rapid metabolism, development of radiolabeled metabolites, high nonspecific binding, unfavorable biodistribution, and poor reproducibility. As a result, the development and clinical validation of radiolabeled drugs is very expensive and time-consuming and cannot yet be used on a large scale (21).

Nevertheless PET using radiolabeled taxanes is a promising technique for several investigations (66). First, PET studies using [^{18}F]paclitaxel and [^{11}C]docetaxel may serve as a good surrogate marker for MDR function (67), as these drugs can show *in vivo* functionality of MDR transporters in tumors. Second, effects of other (anticancer) drugs, including antiangiogenic drugs and inhibitors of ABCB1, on delivery of radiolabeled taxanes to tumors can be explored *in vivo*. In particular, such PET studies may help to define the optimal design of large clinical trials to investigate the effects of drug scheduling on efficacy in patients with cancer. Third, when complexity of these PET studies can be reduced in the future, radiolabeled taxanes may be useful to predict response to taxane therapy and become a clinical tool for selecting patients for taxane-containing treatment strategies, thereby contributing to a more personalized treatment strategy. Finally, results obtained from the studies on [^{18}F]paclitaxel and [^{11}C]docetaxel provide a framework for the development and clinical validation of other radiolabeled taxanes and other anticancer drugs. Because [^{18}F]paclitaxel and [^{11}C]docetaxel were developed at least 10 years after the approval of the corresponding drugs, data obtained can easily be linked to widespread clinical observations. As mentioned previously, the published results from studies on [^{18}F]paclitaxel and [^{11}C]docetaxel seem to fit and explain the observed clinical behavior of paclitaxel and docetaxel, respectively, in patients with cancer. As discussed in this *CCR Focus* section, other techniques, including circulating tumor cells, circulating biomarkers, and single-nucleotide polymorphisms, can also provide more insight into the pharmacokinetics and pharmacodynamics of taxanes (68–71). For newly developed taxanes, future PET studies using radiolabeled taxanes could serve as pre-phase I studies (72). Before conventional phase I studies, such PET studies should provide pharmacokinetic and

pharmacodynamic data, potentially accelerating the early clinical development of new taxanes.

Conclusions

PET using radiolabeled anticancer drugs is a promising method to further understand the clinical behavior of these agents. In addition, it may contribute to better guided treatment planning in individual patients with cancer. In the present review, data available for the labeled taxanes [^{18}F]paclitaxel and [^{11}C]docetaxel are discussed and linked to clinical observations following paclitaxel and docetaxel therapy, respectively. On the basis of their biodistribution, [^{18}F]paclitaxel and [^{11}C]docetaxel may be useful tracers to characterize drug delivery in tumors located in the thoracic region, including breast cancer and lung cancer. Human PET studies using [^{18}F]paclitaxel and [^{11}C]docetaxel have provided data that may better explain toxicity and efficacy of paclitaxel and docetaxel. In addition, another [^{11}C]docetaxel PET study has shown that other anticancer drugs, such as antiangiogenic drugs, can affect delivery of taxanes to tumors. Experience gained with [^{18}F]paclitaxel and [^{11}C]docetaxel may be extrapolated to other taxanes and may provide a framework for the development and clinical implementation of other radiolabeled anticancer drugs, even outside the taxane era.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: A.A.M. van der Veldt, A.A. Lammertsma
Development of methodology: A.A.M. van der Veldt, A.A. Lammertsma
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.A.M. van der Veldt
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.A.M. van der Veldt
Writing, review, and/or revision of the manuscript: A.A.M. van der Veldt, A.A. Lammertsma
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.A.M. van der Veldt
Study supervision: A.A.M. van der Veldt, A.A. Lammertsma

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