

Case Report

Advanced multimodality contouring in
Radiation Therapy
with *syngo.via* RT Image Suite

Authors: Marcello Sabatino, Vincent Jöst, Julia Sudmann, Birgit Naß-Beck, Matthias Kretschmer, Florian Würschmidt,
Radiologische Allianz Hamburg, Germany

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Introduction

In addition to further developments in hardware technology, software solutions for radiation therapy planning are required that optimize structure delineation based on multimodality imaging. A recent paper by Cyran et al. emphasized the role of tailored imaging in radiation therapy planning. Any improvements in the field of imaging will impact radiation oncology per se [1].

Computed tomography (CT) forms the basis of modern radiation therapy planning thanks to its ability to encode objects in spatial electron density distributions. Only CT can determine the attenuation coefficients per voxel in a patient's body with the high degree of reliability required by dose calculation algorithms in treatment planning systems (TPS) [2]. Clinicians primarily use CT images to delineate planning target volumes (PTV) and organs at risk (OAR), which can be supplemented by coregistered magnetic resonance

imaging (MRI) data in accordance with the indications. For example, in the absence of soft-tissue contrast. The use of MRI images to provide attenuation information, commonly known as MRI-only radiation therapy, is currently the subject of numerous research projects [3][4].

In addition to MRI, positron emission tomography (PET)/CT images have become an established, routine component of staging and therapy planning in radiation oncology [5]. Traditionally, all of the required imaging information is transferred to the TPS and coregistered with the initial planning CT either rigidly or, in selected cases, deformably. Usually only one image series fused to another series can be displayed, such as a CT to MRI fusion, for example. However, the anatomically correctly correlated, simultaneous display of all of the datasets needed to delineate the PTV would be more useful. In the context of respiratory

management, it may be beneficial to concurrently view multiple studies, particularly when using time-resolved planning datasets.

It would be optimal to contour or edit structures in all of the assigned image studies in any anatomic orientation. Modern treatment planning systems are normally limited to one monitor – which results in inferior image quality. This limitation has disadvantages not only for radiation planning, but also for post-therapy follow-up or restaging. As a result of these limitations, follow-up or restaging assessments frequently do not take place in the TPS but rather in a PACS viewer.

This study investigates the clinical usability of the software version VB20 of the syngo.via RT Image Suite in the context of the above-mentioned expanded modern radiation therapy planning requirements [6].

Technical aspects

syngo.via RT Image Suite is based on *syngo.via*, Siemens' platform for all medical imaging applications.

syngo.via RT Image Suite was designed to enable the efficient use of multimodality imaging in radiation therapy. It allows easy access to the PACS system using a query and retrieve interface.

In addition, a prefetching option allows studies to be automatically transferred to selected clients and assigned predefined workflows. After the datasets

have been successfully contoured for therapy planning, connectivity to the TPS or another node via DICOM export is available (see Figure 1).

Images from any modality are transmitted to the central PACS server using auto-transfer. Between different facilities, data can be retrieved by the *syngo* server from local clients. If necessary, ConeBeam CTs (CBCTs) can be transferred automatically to the server using prefetching. Data that is ready for planning is transferred to the TPS by DICOM export.

Scans from various imaging modalities such as CT, MRI, and PET/CT can be displayed in *syngo.via* RT Image Suite. Up to four single (or four fused) image studies can be displayed for one patient in parallel, across four panes (see Figure 2).

All displayed image studies are automatically rigidly coregistered when the image is loaded.

syngo.via RT Image Suite with a dual monitor configuration is shown above: the primary planning CT

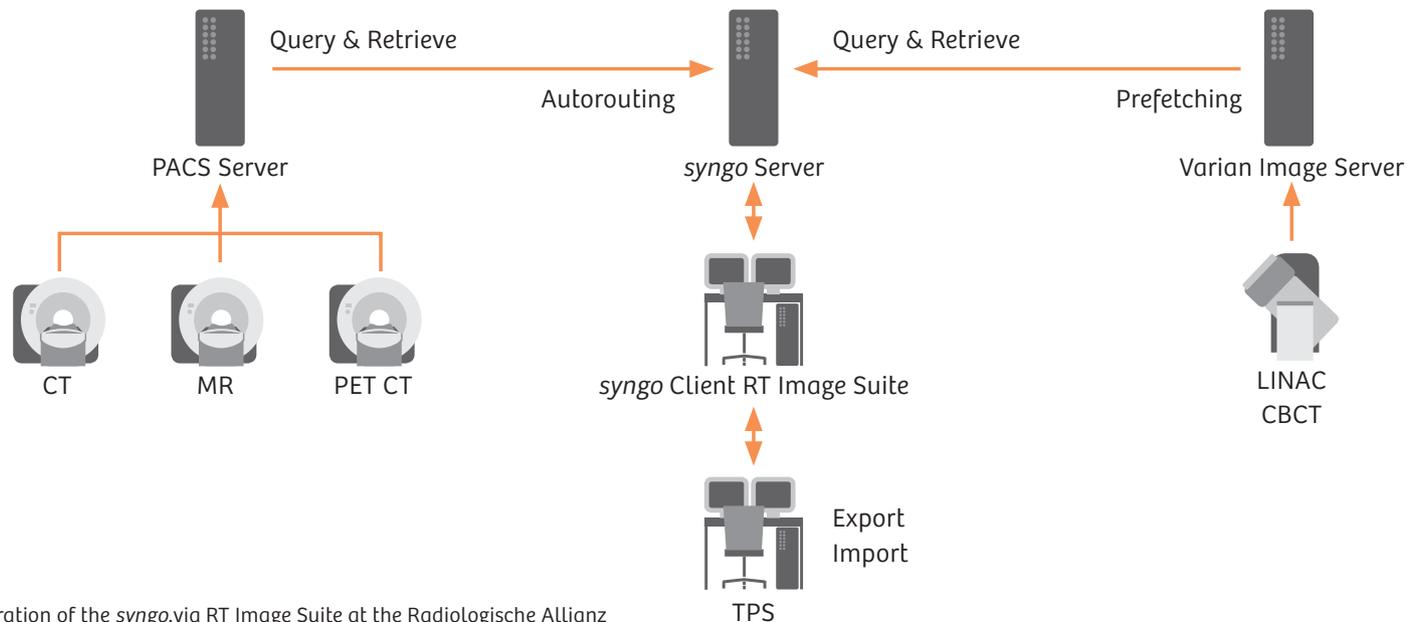


Figure 1: System configuration of the *syngo.via* RT Image Suite at the Radiologische Allianz

study is on the left, registered to three MRI image studies on the right.

When inconsistent tabletops have been used, for example curved tabletops for diagnostic images, deformable registration may be used.

PET data, normally interlocked with the associated CT scan, can be projected onto any other image

dataset by registering the associated CT with another image series, for example with the planning CT.

Contouring is not limited to the main image study (this is normally the planning CT); it can be performed on every coregistered image, regardless of modality.

If needed, structures created in one study can be mirrored in other studies for further refinement, for example with an MRI sequence.

Contours are saved as a structure set belonging to the user-selected study, typically the primary study. In addition, CBCTs can be automatically imported into the syngo.via RT Image Suite from the TPS database using prefetching or by importing images from external media. If required, image studies can be anonymized for study purposes.

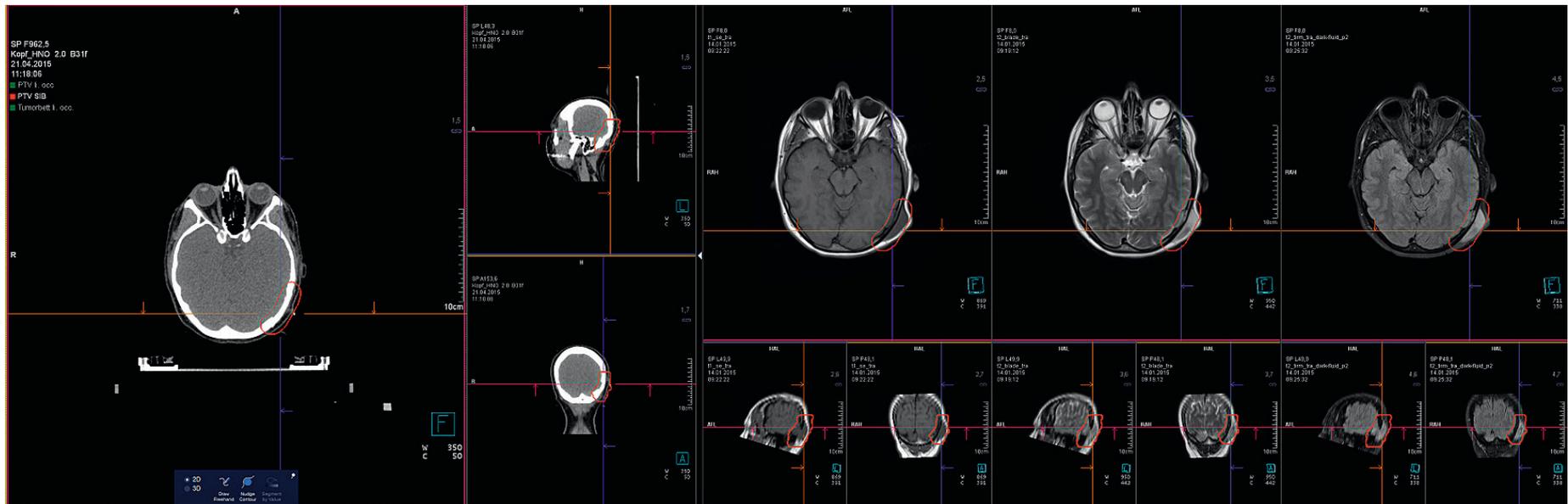


Figure 2: Screen grab of a dual monitor workstation with the syngo.via RT Image Suite application. Courtesy of Radiologische Allianz Hamburg, Germany

Case 1: SBRT of the lung

A 73-year-old patient with initial non-small cell lung cancer (NSCLC) in the left superior lobe (staging: pT1b pN0 L0 V0 R0 G2) was to receive fractionated stereotactic body radiotherapy (SBRT) to the right inferior lobe. The planned therapy was comprised of four to five fractions per week with a 7 Gy single dose (SD) and up to 70 Gy total dose (TD). Planning was carried out using VMAT technology and respiratory gating (gated CT with respiration monitoring, no phase triggering). Phase-based CT datasets of 0% – 100% (in 10% increments) and the resulting average CT image were generated for the planning process. A vacuum mattress for immobilization as well as the Varian RPM™ gating system were used. A diagnostic PET/CT was performed on a curved tabletop.

In *syngo.via* RT Image Suite, the procedure was as follows:

- The average CT image was used as the primary study for dose calculation
- Due to the small size of the lesion, PET/CT was loaded
- Afterwards, the internal target volume (ITV) was contoured directly on the average CT image

Despite differences in patient positioning, the result achieved by the rigid fusion was sufficient for identifying the PET enhancing tissue in this case.

The result of the rigid registration of the CT dataset with the average CT image is illustrated here (Figure 3). In addition to displaying the PET data on the associated CT image, the PET data can also be fused onto the average CT image.

The fact that the PET data could be fused directly onto the planning dataset proved to be advantageous in this case. It would normally not have been possible to display the average CT image fused onto the PET study – including the associated CT image – in the TPS. Without *syngo.via* RT Image Suite, our workflow required either a TPS and PACS viewer next to one another or the creation of an additional structure on the PET/CT to be used as a “supporting structure”.

With *syngo.via* RT Image Suite, we can significantly streamline the contouring workflow for such patients.

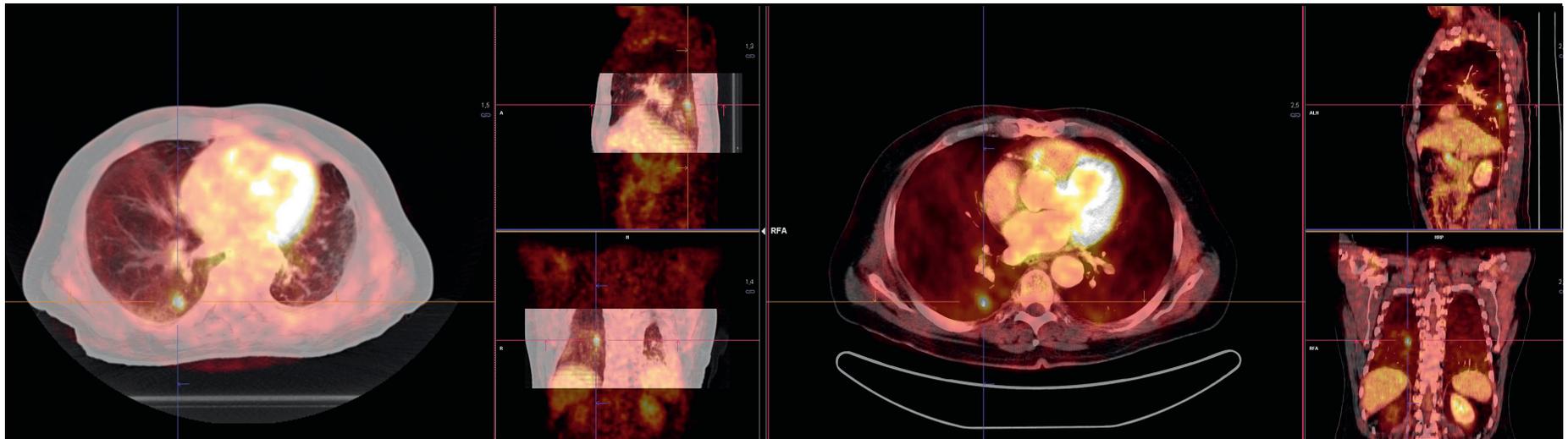


Figure 3:
Registration of treatment planning CT and diagnostic PET/CT: Crosshairs show the position of the gross tumor volume

Left: Average CT sequence with vacuum mattress fused with the PET data

Right: Rigidly coregistered diagnostic PET/CT

Courtesy of Radiologische Allianz Hamburg, Germany

Case 2: Liver SBRT of a NSCLC patient

A 67-year-old oligometastatic left-sided NSCLC patient was to have an SBRT of the liver. The planned therapy was comprised of fractionated stereotactic radiotherapy using VMAT technology and imaging (IGRT) of the liver lesion in segment 4b on the left side. The prescribed dose of 7 Gy SD was delivered four times per week, up to 70 Gy TD.

CT studies with different respiratory phases, native free breathing and contrast agent phases during inspiration, expiration, and midline were generated for planning purposes. A vacuum mattress was used as a positioning aid. Furthermore, an MRI was performed in the planning position (flat tabletop without positioning aids) to identify the hepatic focal finding with suspected metastases. It was possible to use a diagnostic F18-FDG* PET/CT (patient positioning with a curved tabletop) as an additional modality.

The procedure in *syngo.via* RT Image Suite was as follows:

- The native free-breathing CT was used as the primary study
- The ITV was contoured directly on all of the contrast agent planning CT phases
- As the lesion was enriched with only a little contrast agent, a PET/CT was used for tumor position verification
- The latter was achieved by deforming the CT of the PET study and subsequently fusing the PET data with the primary study
- After localization, a deformable registration of a T1-weighted MRI image with a contrast agent-enhanced planning CT study was carried out in order to obtain a better impression of the size of the metastases in the noisy planning CT image (see Figure 4)

After this, the ITV was contoured using the contrast agent CT studies with simultaneous mirroring of the contour onto the native free-breathing study. After contouring, it was possible to directly check the ITVs with reference to the three contrast agent phases, as well as the MRI and PET/CT data, in all three orientations. The registration results of the planning CT with a contrast agent phase, an MRI sequence, and the PET/CT are shown. Elastic registrations had to be used due to the partial use of an abdominal press.

In this case, the elastic registration proved to be advantageous. Thanks to the deformation of the MRI and PET data, we were able to obtain additional information on the localization and size of the lesion. In the TPS, however, the contouring of the GTVs would have been performed on the 3 contrast agent CT phases, since rigid registrations with the modalities without an abdominal press would not have delivered a sufficiently precise result in this case.

* For indications and usage information for Fludeoxyglucose F 18 Injection (18F FDG) see page 2. For full prescribing information see pages 13-15 .

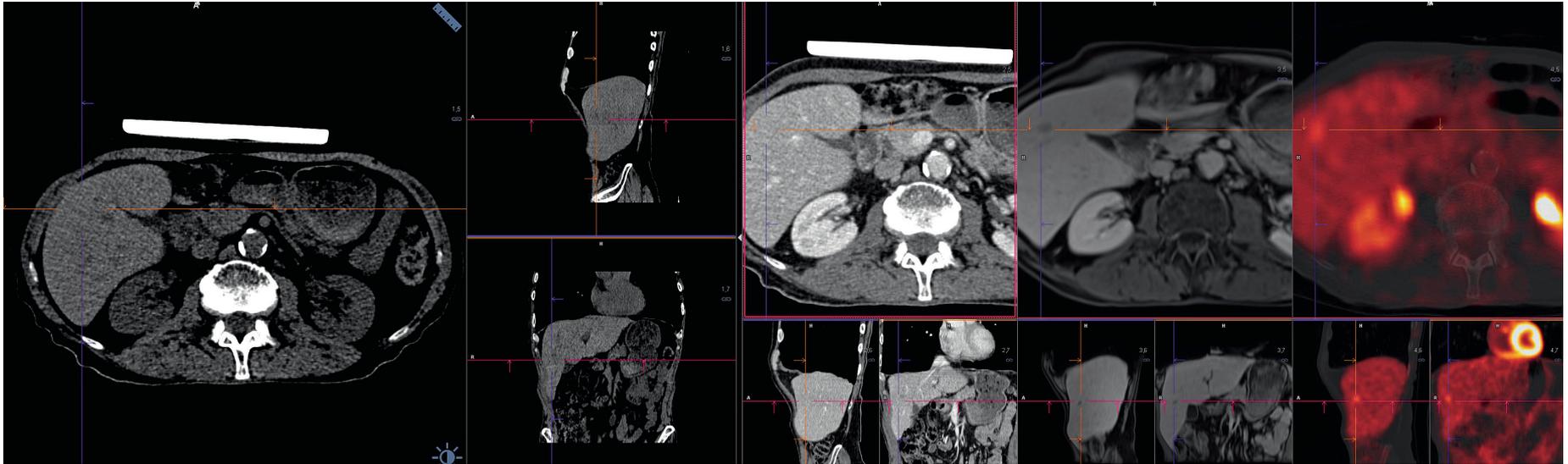


Figure 4:
View of the elastic registration results of multimodal liver SBRT planning

From left to right:
Average planning CT, contrast-enhanced CT and T1-weighted MRI data as well as PET/CT data

Courtesy of Radiologische Allianz Hamburg, Germany

Case 3: Follow-up of a NSCLC patient

A fractionated SBRT with a scheme of 10 x 6 Gy was applied to the left lung of a 60-year-old patient with NSCLC. In the course of follow-up, CT scans were to be performed at three-month intervals and transferred to the *syngo* database.

The response during the entire follow-up can be assessed at a glance. The projection of the initial GTVs onto the follow-up CT scans is advantageous (see Figure 5). Additional follow-up results obtained in the future can be input into the database successively.

Having four datasets side-by-side enables an easy assessment of treatment efficacy without the need to perform sequential assessments in the PACS viewer or TPS.

syngo.via RT Image Suite saved time and reduced the risk of errors when comparing structures.

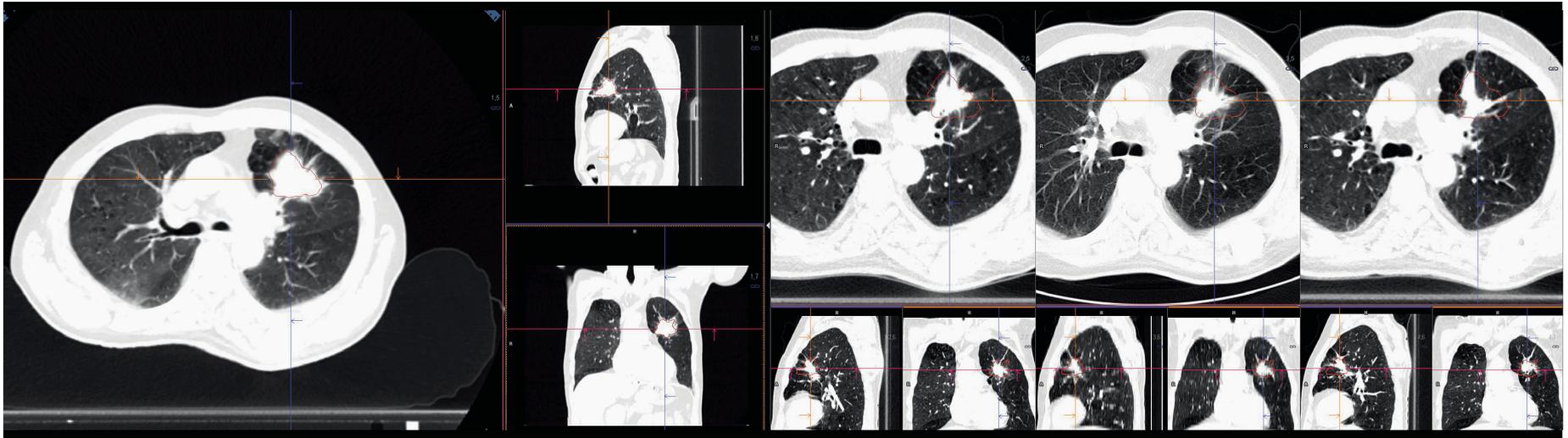


Figure 5:

View of the registration results of the planning and follow-up CT scans

From left to right: The initial planning CT scan, along with the follow-up CT scans from three, six, and nine months after the RT.

The initial gross tumor volume (GTV) is projected onto all the datasets

Courtesy of Radiologische Allianz Hamburg, Germany

Conclusion

With *syngo.via* RT Image Suite and its capacity to display up to eight datasets simultaneously, the full potential of multimodality imaging from various imaging methods can be realized. Editing structures superimposed over any image series and instantly observing changes was perceived as being tremendously helpful.

In all of the cases, the time required to contour using *syngo.via* RT Image Suite was at least equivalent to or faster than our TPS since it could display all of the image series concurrently and contour them at the same time using parallel contouring – rather than requiring sequential contouring in the TPS. As TPSs are oriented towards planning datasets, additional modalities have to be superimposed/projected onto the primary dataset in succession. Since the TPS is optimized for therapy planning, follow-up checks are not adequately supported. Image retrieval from the image archive can be time consuming; image viewing is often restricted to viewing a maximum of two image series as a fused image, and then requires blending to switch between images. As a result, response to therapy is normally assessed using a PACS viewer in radiology, but this has the disadvantage that the RT structure sets often cannot be loaded.

In *syngo.via* RT Image Suite, all datasets needed for follow-up checks are available via prefetching from the image archive. Furthermore, eight image series can be visualized concurrently (four single series or four fused series) including RT structure sets, which simplifies follow-up checks. Fusion accuracy was rated as clinically suitable by the participating radiation therapists. The deformable image registration was also used for cases where the positioning and immobilization of the patient deviated significantly, such as in the SBRT of the liver.

Vorwerk et al. have defined requirements that should be fulfilled by software regarding data import, registration and contouring for highly conformal radiation treatment. The requirements are divided into categories for safety, accuracy and efficiency. These functionalities are then further divided into three groups ranging from minimal to enhanced and optimal requirements (best possible feature). Most of the enhanced and optimal requirements were met by the *syngo.via* RT Image Suite; for example, it fulfilled the optimal requirement for flexible registration between different datasets [8].

The direct connection between the PACS system and *syngo.via* RT Image Suite enables better streamlining of certain workflows for the radiation oncologist. User-defined prefetching means that the latest study is directly available and already registered to the planning dataset. This workflow accelerates the evaluation of the current study with respect to former GTV/CTV contours. In a treatment planning system, these steps must be done manually, which makes the workflow impractical in clinical routine. Most clinics do not have access to synchronic image acquisitions such as PET/MRI on a broad basis. *syngo.via* RT Image Suite provides an alternative, allowing clinicians to obtain synergies by enabling the concurrent registration and viewing of multiple modalities and creating a kind of “virtual PET/MRI”. Working with *syngo.via* RT Image Suite proved to be efficient and meant we could streamline the contouring and follow up workflows in our department.

References

- [1] Cyran C et al. Visualization, imaging and new preclinical diagnostics in radiation oncology. *Radiation Oncology* 2014 9:3
- [2] Gisele C. Pereira et al. The Role of Imaging in Radiation Therapy Planning: Past, Present, and Future. *Journal of BioMed Research International*, Article number Article ID 231090, April 2014
- [3] Johansson A et al. CT substitute derived from MRI sequences with ultrashort echo time. *Med Phys.* 2011 38(5):2708-14
- [4] Hsu SH et al. Investigation of a method for generating synthetic CT models from MRI scans of the head and neck for radiation therapy. *Phys Med Biol.* 2013 58(23):8419-35
- [5] Thorwarth D Functional imaging for radiotherapy treatment planning: current status and future directions-a review. *Br J Radiol.* 2015 88(1051):20150056
- [6] syngo.via RT Image Suite VB20, as of September 2017
- [7] The statements by Siemens' customers described herein are based on results that were achieved in the customer's unique setting. Since there is no "typical" hospital and many variables exist (e.g., hospital size, case mix, level of IT adoption) there can be no guarantee that other customers will achieve the same results.
- [8] Vorwerk et al. Making the right software choice for clinically used equipment in radiation oncology. *Radiation Oncology* 2014 9:145

Fludeoxyglucose F 18 Injection, USP

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Fludeoxyglucose F 18 Injection safely and effectively. See full prescribing information for Fludeoxyglucose F 18 Injection.

Fludeoxyglucose F 18 Injection, USP

For intravenous use

Initial U.S. Approval: 2005

RECENT MAJOR CHANGES

Warnings and Precautions

(5.1, 5.2) 7/2010

Adverse Reactions (6) 7/2010

INDICATIONS AND USAGE

Fludeoxyglucose F18 Injection is indicated for positron emission tomography (PET) imaging in the following settings:

- **Oncology:** For assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.
- **Cardiology:** For the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging.
- **Neurology:** For the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures (1).

DOSAGE AND ADMINISTRATION

Fludeoxyglucose F 18 Injection emits radiation. Use procedures to minimize radiation exposure. Screen for blood glucose abnormalities.

- In the oncology and neurology settings, instruct patients to fast for 4 to 6 hours prior to the drug's injection. Consider medical therapy and laboratory testing to assure at least two days of normoglycemia prior to the drug's administration (5.2).
- In the cardiology setting, administration of glucose-containing food or liquids (e.g., 50 to 75 grams) prior to the drug's injection facilitates localization of cardiac ischemia (2.3).

Aseptically withdraw Fludeoxyglucose F 18 Injection from its container and administer by intravenous injection (2).

The recommended dose:

- for adults is 5 to 10 mCi (185 to 370 MBq), in all indicated clinical settings (2.1).
- for pediatric patients is 2.6 mCi in the neurology setting (2.2). Initiate imaging within 40 minutes following drug injection; acquire static emission images 30 to 100 minutes from time of injection (2).

DOSAGE FORMS AND STRENGTHS

Multi-dose 30mL and 50mL glass vial containing 0.74 to 7.40 GBq/mL (20 to 200 mCi/mL) Fludeoxyglucose F 18 Injection and 4.5 mg of sodium chloride with 0.1 to 0.5% w/w ethanol as a stabilizer (approximately 15 to 50 mL volume) for intravenous administration (3).

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Radiation risks: use smallest dose necessary for imaging (5.1).
- Blood glucose abnormalities: may cause suboptimal imaging (5.2).

ADVERSE REACTIONS

Hypersensitivity reactions have occurred; have emergency resuscitation equipment and personnel immediately available (6).

To report SUSPECTED ADVERSE REACTIONS, contact PETNET Solutions, Inc. at 877-473-8638 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Pregnancy Category C: No human or animal data. Consider alternative diagnostics; use only if clearly needed (8.1).

- Nursing mothers: Use alternatives to breast feeding (e.g., stored breast milk or infant formula) for at least 10 half-lives of radioactive decay, if Fludeoxyglucose F 18 Injection is administered to a woman who is breast-feeding (8.3).
- Pediatric Use: Safety and effectiveness in pediatric patients have not been established in the oncology and cardiology settings (8.4).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 1/2016

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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Fludeoxyglucose F 18 Injection is indicated for positron emission tomography (PET) imaging in the following settings:

1.1 Oncology

For assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.

1.2 Cardiology

For the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging.

1.3 Neurology

For the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.

2 DOSAGE AND ADMINISTRATION

Fludeoxyglucose F 18 Injection emits radiation. Use procedures to minimize radiation exposure. Calculate the final dose from the end of synthesis (EOS) time using proper radioactive decay factors. Assay the final dose in a properly calibrated dose calibrator before administration to the patient [see Description (11.2)].

2.1 Recommended Dose for Adults

Within the oncology, cardiology and neurology settings, the recommended dose for adults is 5 to 10 mCi (185 to 370 MBq) as an intravenous injection.

2.2 Recommended Dose for Pediatric Patients

Within the neurology setting, the recommended dose for pediatric patients is 2.6 mCi, as an intravenous injection. The optimal dose adjustment on the basis of body size or weight has not been determined [see Use in Special Populations (8.4)].

2.3 Patient Preparation

- To minimize the radiation absorbed dose to the bladder, encourage adequate hydration. Encourage the patient to drink water or other fluids (as tolerated) in the 4 hours before their PET study.
- Encourage the patient to void as soon as the imaging study is completed and as often as possible thereafter for at least one hour.
- Screen patients for clinically significant blood glucose abnormalities by obtaining a history and/or laboratory tests [see Warnings and Precautions (5.2)]. Prior to Fludeoxyglucose F 18 PET imaging in the oncology and neurology settings, instruct patient to fast for 4 to 6 hours prior to the drug's injection.
- In the cardiology setting, administration of glucose-containing food or liquids (e.g., 50 to 75 grams) prior to Fludeoxyglucose F18 Injection facilitates localization of cardiac ischemia

2.4 Radiation Dosimetry

The estimated human absorbed radiation doses (rem/mCi) to a newborn (3.4 kg), 1-year old (9.8 kg), 5-year old (19 kg), 10-year old (32 kg), 15-year old (57 kg), and adult (70 kg) from intravenous administration of Fludeoxyglucose F 18 Injection are shown in Table 1. These estimates were calculated based on human² data and using the data published by the International Commission on Radiological Protection⁴ for Fludeoxyglucose ¹⁸F. The dosimetry data show that there are slight variations in absorbed radiation dose for various organs in each of the age groups. These dissimilarities in absorbed radiation dose are due to developmental age variations (e.g., organ size, location, and overall metabolic rate for each age group). The identified critical organs (in descending order) across all age groups evaluated are the urinary bladder, heart, pancreas, spleen, and lungs.

Table 1. Estimated Absorbed Radiation Doses (rem/mCi) After Intravenous Administration of Fludeoxyglucose F-18 Injection^a

| Organ | New-born | 1-year old | 5-year old | 10-year old | 15-year old | Adult |
|---------------------------|----------|------------|------------|-------------|-------------|---------|
| | (3.4 kg) | (9.8 kg) | (19 kg) | (32 kg) | (57 kg) | (70 kg) |
| Bladder wall ^b | 4.3 | 1.7 | 0.93 | 0.60 | 0.40 | 0.32 |
| Heart wall | 2.4 | 1.2 | 0.70 | 0.44 | 0.29 | 0.22 |
| Pancreas | 2.2 | 0.68 | 0.33 | 0.25 | 0.13 | 0.096 |
| Spleen | 2.2 | 0.84 | 0.46 | 0.29 | 0.19 | 0.14 |
| Lungs | 0.96 | 0.38 | 0.20 | 0.13 | 0.092 | 0.064 |
| Kidneys | 0.81 | 0.34 | 0.19 | 0.13 | 0.089 | 0.074 |
| Ovaries | 0.80 | 0.8 | 0.19 | 0.11 | 0.058 | 0.053 |
| Uterus | 0.70 | 0.35 | 0.19 | 0.12 | 0.076 | 0.062 |
| LLI wall [*] | 0.69 | 0.28 | 0.15 | 0.097 | 0.060 | 0.051 |
| Liver | 0.69 | 0.31 | 0.17 | 0.11 | 0.076 | 0.058 |
| Gallbladder wall | 0.69 | 0.26 | 0.14 | 0.093 | 0.059 | 0.049 |
| Small intestine | 0.68 | 0.29 | 0.15 | 0.096 | 0.060 | 0.047 |
| ULI wall ^{**} | 0.67 | 0.27 | 0.15 | 0.090 | 0.057 | 0.046 |
| Stomach wall | 0.65 | 0.27 | 0.14 | 0.089 | 0.057 | 0.047 |
| Adrenals | 0.65 | 0.28 | 0.15 | 0.095 | 0.061 | 0.048 |
| Testes | 0.64 | 0.27 | 0.14 | 0.085 | 0.052 | 0.041 |
| Red marrow | 0.62 | 0.26 | 0.14 | 0.089 | 0.057 | 0.047 |
| Thymus | 0.61 | 0.26 | 0.14 | 0.086 | 0.056 | 0.044 |
| Thyroid | 0.61 | 0.26 | 0.13 | 0.080 | 0.049 | 0.039 |
| Muscle | 0.58 | 0.25 | 0.13 | 0.078 | 0.049 | 0.039 |
| Bone surface | 0.57 | 0.24 | 0.12 | 0.079 | 0.052 | 0.041 |
| Breast | 0.54 | 0.22 | 0.11 | 0.068 | 0.043 | 0.034 |
| Skin | 0.49 | 0.20 | 0.10 | 0.060 | 0.037 | 0.030 |
| Brain | 0.29 | 0.13 | 0.09 | 0.078 | 0.072 | 0.070 |
| Other tissues | 0.59 | 0.25 | 0.13 | 0.083 | 0.052 | 0.042 |

^a MIRDOSE 2 software was used to calculate the radiation absorbed dose. Assumptions on the biodistribution based on data from Gallagher et al.¹ and Jones et al.²

^b The dynamic bladder model with a uniform voiding frequency of 1.5 hours was used.

^{*} LLI = lower large intestine;

^{**} ULI = upper large intestine

Fludeoxyglucose F 18 Injection, USP

2.5 Radiation Safety – Drug Handling

- Use waterproof gloves, effective radiation shielding, and appropriate safety measures when handling Fludeoxyglucose F 18 Injection to avoid unnecessary radiation exposure to the patient, occupational workers, clinical personnel and other persons.
- Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.
- Calculate the final dose from the end of synthesis (EOS) time using proper radioactive decay factors. Assay the final dose in a properly calibrated dose calibrator before administration to the patient [see Description (11.2)].
- The dose of Fludeoxyglucose F 18 used in a given patient should be minimized consistent with the objectives of the procedure, and the nature of the radiation detection devices employed.

2.6 Drug Preparation and Administration

- Calculate the necessary volume to administer based on calibration time and dose.
- Aseptically withdraw Fludeoxyglucose F 18 Injection from its container.
- Inspect Fludeoxyglucose F 18 Injection visually for particulate matter and discoloration before administration, whenever solution and container permit.
- Do not administer the drug if it contains particulate matter or discoloration; dispose of these unacceptable or unused preparations in a safe manner, in compliance with applicable regulations.
- Use Fludeoxyglucose F 18 Injection within 12 hours from the EOS.

2.7 Imaging Guidelines

- Initiate imaging within 40 minutes following Fludeoxyglucose F 18 Injection administration.
- Acquire static emission images 30 to 100 minutes from the time of injection.

3 DOSAGE FORMS AND STRENGTHS

Multiple-dose 30 mL and 50 mL glass vial containing 0.74 to 7.40 GBq/mL (20 to 200 mCi/mL) of Fludeoxyglucose F 18 Injection and 4.5 mg of sodium chloride with 0.1 to 0.5% w/w ethanol as a stabilizer (approximately 15 to 50 mL volume) for intravenous administration.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Radiation Risks

Radiation-emitting products, including Fludeoxyglucose F 18 Injection, may increase the risk for cancer, especially in pediatric patients. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker [see Dosage and Administration (2.5)].

5.2 Blood Glucose Abnormalities

In the oncology and neurology setting, suboptimal imaging may occur in patients with inadequately regulated blood glucose levels. In these patients, consider medical therapy and laboratory testing to assure at least two days of normoglycemia prior to Fludeoxyglucose F 18 Injection administration.

6 ADVERSE REACTIONS

Hypersensitivity reactions with pruritus, edema and rash have been reported in the post-marketing setting. Have emergency resuscitation equipment and personnel immediately available.

7 DRUG INTERACTIONS

The possibility of interactions of Fludeoxyglucose F 18 Injection with other drugs taken by patients undergoing PET imaging has not been studied.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with Fludeoxyglucose F 18 Injection. It is also not known whether Fludeoxyglucose F 18 Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Consider alternative diagnostic tests in a pregnant woman; administer Fludeoxyglucose F 18 Injection only if clearly needed.

8.3 Nursing Mothers

It is not known whether Fludeoxyglucose F 18 Injection is excreted in human milk. Consider alternative diagnostic tests in women who are breast-feeding. Use alternatives to breast feeding (e.g., stored breast milk or infant formula) for at least 10 half-lives of radioactive decay, if Fludeoxyglucose F 18 Injection is administered to a woman who is breast-feeding.

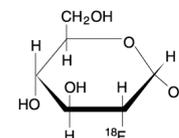
8.4 Pediatric Use

The safety and effectiveness of Fludeoxyglucose F 18 Injection in pediatric patients with epilepsy is established on the basis of studies in adult and pediatric patients. In pediatric patients with epilepsy, the recommended dose is 2.6 mCi. The optimal dose adjustment on the basis of body size or weight has not been determined. In the oncology or cardiology settings, the safety and effectiveness of Fludeoxyglucose F 18 Injection have not been established in pediatric patients.

11 DESCRIPTION

11.1 Chemical Characteristics

Fludeoxyglucose F 18 Injection is a positron emitting radio-pharmaceutical that is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. The active ingredient 2-deoxy-2-¹⁸F]fluoro-D-glucose has the molecular formula of C₆H₁₁¹⁸FO₅ with a molecular weight of 181.26, and has the following chemical structure:



Fludeoxyglucose F 18 Injection is provided as a ready to use sterile, pyrogen free, clear, colorless solution. Each mL contains between 0.740 to 7.40 GBq (20.0 to 200 mCi) of 2-deoxy-2-¹⁸F]fluoro-D-glucose at the EOS, 4.5 mg of sodium chloride and 0.1 to 0.5% w/w ethanol as a stabilizer. The pH of the solution is between 4.5 and 7.5. The solution is packaged in a multiple-dose glass vial and does not contain any preservative.

11.2 Physical Characteristics

Fluorine F 18 decays by emitting positron to Oxygen O 16 (stable) and has a physical half-life of 109.7 minutes. The principal photons useful for imaging are the dual 511 keV gamma photons, that are produced and emitted simultaneously in opposite direction when the positron interacts with an electron (Table 2).

| Radiation/Emission | % Per Disintegration | Mean Energy |
|--------------------|----------------------|-------------|
| Positron (b+) | 96.73 | 249.8 keV |
| Gamma (±)* | 193.46 | 511.0 keV |

From: Kocher, D.C. Radioactive Decay Tables DOE/TIC-I 1026, 89 (1981)

The specific gamma ray constant (point source air kerma coefficient) for fluorine F 18 is 5.7 R/hr/mCi (1.35×10^{-6} Gy/hr/kBq) at 1 cm. The half-value layer (HVL) for the 511 keV photons is 4 mm lead (Pb). The range of attenuation coefficients for this radionuclide as a function of lead shield thickness is shown in Table 3. For example, the interposition of an 8 mm thickness of Pb, with a coefficient of attenuation of 0.25, will decrease the external radiation by 75%.

| Shield thickness (Pb) mm | Coefficient of attenuation |
|--------------------------|----------------------------|
| 0 | 0.00 |
| 4 | 0.50 |
| 8 | 0.25 |
| 13 | 0.10 |
| 26 | 0.01 |
| 39 | 0.001 |
| 52 | 0.0001 |

For use in correcting for physical decay of this radionuclide, the fractions remaining at selected intervals after calibration are shown in Table 4.

| Minutes | Fraction Remaining |
|---------|--------------------|
| 0** | 1.000 |
| 15 | 0.909 |
| 30 | 0.826 |
| 60 | 0.683 |
| 110 | 0.500 |
| 220 | 0.250 |

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fludeoxyglucose F 18 is a glucose analog that concentrates in cells that rely upon glucose as an energy source, or in cells whose dependence on glucose increases under pathophysiological conditions. Fludeoxyglucose F 18 is transported through the cell membrane by facilitative glucose transporter proteins and is phosphorylated within the cell to [¹⁸F] FDG-6-phosphate by the enzyme hexokinase. Once phosphorylated it cannot exit until it is dephosphorylated by glucose-6-phosphatase. Therefore, within a given tissue or pathophysiological process, the retention and clearance of Fludeoxyglucose F 18 reflect a balance involving glucose transporter, hexokinase and glucose-6-phosphatase activities. When allowance is made for the kinetic differences between glucose and Fludeoxyglucose F 18 transport and phosphorylation (expressed as the 'lumped constant' ratio), Fludeoxyglucose F 18 is used to assess glucose metabolism. In comparison to background activity of the specific organ or tissue type, regions of decreased or absent uptake of Fludeoxyglucose F 18 reflect the decrease or absence of glucose metabolism. Regions of increased uptake of Fludeoxyglucose F 18 reflect greater than normal rates of glucose metabolism.

12.2 Pharmacodynamics

Fludeoxyglucose F 18 Injection is rapidly distributed to all organs of the body after intravenous administration. After background clearance of Fludeoxyglucose F 18 Injection, optimal PET imaging is generally achieved between 30 to 40 minutes after administration.

In cancer, the cells are generally characterized by enhanced glucose metabolism partially due to (1) an increase in activity of glucose transporters, (2) an increased rate of phosphorylation activity, (3) a reduction of phosphatase activity or, (4) a dynamic alteration in the balance among all these processes. However, glucose metabolism of cancer as reflected by Fludeoxyglucose F 18 accumulation shows considerable variability. Depending on tumor type, stage, and location, Fludeoxyglucose F 18 accumulation may be increased, normal, or decreased. Also, inflammatory cells can have the same variability of uptake of Fludeoxyglucose F 18.

In the heart, under normal aerobic conditions, the myocardium meets the bulk of its energy requirements by oxidizing free fatty acids. Most of the exogenous glucose taken up by the myocyte is converted into glycogen. However, under ischemic conditions, the oxidation of free fatty acids decreases, exogenous glucose becomes the preferred myocardial substrate, glycolysis is stimulated, and glucose taken up by the myocyte is metabolized immediately instead of being converted into glycogen. Under these conditions, phosphorylated Fludeoxyglucose F 18 accumulates in the myocyte and can be detected with PET imaging.

In the brain, cells normally rely on aerobic metabolism. In epilepsy, the glucose metabolism varies. Generally, during a seizure, glucose metabolism increases. Interictally, the seizure focus tends to be hypometabolic.

* Produced by positron annihilation

** Calibration time

Fludeoxyglucose F 18 Injection, USP

12.3 Pharmacokinetics

Distribution: In four healthy male volunteers, receiving an intravenous administration of 30 seconds induration, the arterial blood level profile for Fludeoxyglucose F 18 decayed triexponentially. The effective half-life ranges of the three phases were 0.2 to 0.3 minutes, 10 to 13 minutes with a mean and standard deviation (STD) of 11.6 (±) 1.1 min, and 80 to 95 minutes with a mean and STD of 88 (±) 4 min. Plasma protein binding of Fludeoxyglucose F 18 has not been studied.

Metabolism: Fludeoxyglucose F 18 is transported into cells and phosphorylated to [¹⁸F]-FDG-6-phosphate at a rate proportional to the rate of glucose utilization within that tissue. [F18]-FDG-6-phosphate presumably is metabolized to 2-deoxy-2-[F18]fluoro-6-phospho-D-mannose([F 18] FDM-6-phosphate).

Fludeoxyglucose F 18 Injection may contain several impurities (e.g., 2-deoxy-2-chloro-D-glucose (CLDG)). Biodistribution and metabolism of CLDG are presumed to be similar to Fludeoxyglucose F 18 and would be expected to result in intracellular formation of 2-deoxy-2-chloro-6-phospho-D-glucose (CLDG-6-phosphate) and 2-deoxy-2-chloro-6-phospho-D-mannose (CLDM-6-phosphate). The phosphorylated deoxyglucose compounds are dephosphorylated and the resulting compounds (FDG, FDM, CLDG, and CLDM) presumably leave cells by passive diffusion. Fludeoxyglucose F 18 and related compounds are cleared from non-cardiac tissues within 3 to 24 hours after administration. Clearance from the cardiac tissue may require more than 96 hours. Fludeoxyglucose F 18 that is not involved in glucose metabolism in any tissue is then excreted in the urine.

Elimination: Fludeoxyglucose F 18 is cleared from most tissues within 24 hours and can be eliminated from the body unchanged in the urine. Three elimination phases have been identified in the reviewed literature. Within 33 minutes, a mean of 3.9% of the administered radioactive dose was measured in the urine. The amount of radiation exposure of the urinary bladder at two hours post-administration suggests that 20.6% (mean) of the radioactive dose was present in the bladder.

Special Populations: The pharmacokinetics of Fludeoxyglucose F 18 Injection have not been studied in renally-impaired, hepatically impaired or pediatric patients.

Fludeoxyglucose F 18 is eliminated through the renal system. Avoid excessive radiation exposure to this organ system and adjacent tissues.

The effects of fasting, varying blood sugar levels, conditions of glucose intolerance, and diabetes mellitus on Fludeoxyglucose F 18 distribution in humans have not been ascertained [see Warnings and Precautions (5.2)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been performed to evaluate the Fludeoxyglucose F 18 Injection carcinogenic potential, mutagenic potential or effects on fertility.

14 CLINICAL STUDIES

14.1 Oncology

The efficacy of Fludeoxyglucose F 18 Injection in positron emission tomography cancer imaging was demonstrated in 16 independent studies. These studies prospectively evaluated the use of Fludeoxyglucose F 18 in patients with suspected or known malignancies, including non-small cell lung cancer, colo-rectal, pancreatic, breast, thyroid, melanoma, Hodgkin's and non-Hodgkin's lymphoma, and various types of metastatic cancers to lung, liver, bone, and axillary nodes. All these studies had at least 50 patients and used pathology as a standard of truth. The Fludeoxyglucose F 18 Injection doses in the studies ranged from 200 MBq to 740 MBq with a median and mean dose of 370 MBq.

In the studies, the diagnostic performance of Fludeoxyglucose F 18 Injection varied with the type of cancer, size of cancer, and other clinical conditions. False negative and false positive scans were observed. Negative Fludeoxyglucose F 18 Injection PET scans do not exclude the diagnosis of cancer. Positive Fludeoxyglucose F 18 Injection PET scans can not replace pathology to establish a diagnosis of cancer. Non-malignant conditions such as fungal infections, inflammatory processes and benign tumors have patterns of increased glucose metabolism that may give rise to false-positive scans. The efficacy of Fludeoxyglucose F 18 Injection PET imaging in cancer screening was not studied.

14.2 Cardiology

The efficacy of Fludeoxyglucose F 18 Injection for cardiac use was demonstrated in ten independent, prospective studies of patients with coronary artery disease and chronic left ventricular systolic dysfunction who were scheduled to undergo coronary revascularization. Before revascularization, patients underwent PET imaging with Fludeoxyglucose F 18 Injection (74 to 370 MBq, 2 to 10 mCi) and perfusion imaging with other diagnostic radiopharmaceuticals. Doses of Fludeoxyglucose F 18 Injection ranged from 74 to 370 MBq (2 to 10 mCi). Segmental, left ventricular, wall-motion assessments of asynergic areas made before revascularization were compared in a blinded manner to assessments made after successful revascularization to identify myocardial segments with functional recovery.

Left ventricular myocardial segments were predicted to have reversible loss of systolic function if they showed Fludeoxyglucose F 18 accumulation and reduced perfusion (i.e., flow-metabolism mismatch). Conversely, myocardial segments were predicted to have irreversible loss of systolic function if they showed reductions in both Fludeoxyglucose F 18 accumulation and perfusion (i.e., matched defects). Findings of flow-metabolism mismatch in a myocardial segment may suggest that successful revascularization will restore myocardial function in that segment. However, false-positive tests occur regularly, and the decision to have a patient undergo revascularization should not be based on PET findings alone. Similarly, findings of a matched defect in a myocardial segment may suggest that myocardial function will not recover in that segment, even if it is successfully revascularized. However, false-negative tests occur regularly, and the decision to recommend against coronary revascularization, or to recommend a cardiac transplant, should not be based on PET findings alone. The reversibility of segmental dysfunction as predicted with Fludeoxyglucose F 18 PET imaging depends on successful coronary revascularization. Therefore, in patients with a low likelihood of successful revascularization, the diagnostic usefulness of PET imaging with Fludeoxyglucose F 18 Injection is more limited.

14.3 Neurology

In a prospective, open label trial, Fludeoxyglucose F 18 Injection was evaluated in 86 patients with epilepsy. Each patient received a dose of Fludeoxyglucose F 18 Injection in the range of 185 to 370 MBq (5 to 10 mCi). The mean age was 16.4 years (range: 4 months to 58 years; of these, 42 patients were less than 12 years and 16 patients were less than 2 years old). Patients had a known diagnosis of complex partial epilepsy and were under evaluation for surgical treatment of their seizure disorder. Seizure foci had been previously identified on ictal EEGs and sphenoidal EEGs. Fludeoxyglucose F 18 Injection PET imaging confirmed previous diagnostic findings in 16% (14/87) of the patients; in 34% (30/87) of the patients, Fludeoxyglucose F 18 Injection PET images provided new findings. In 32% (27/87), imaging with Fludeoxyglucose F 18 Injection was inconclusive. The impact of these imaging findings on clinical outcomes is not known. Several other studies comparing imaging with Fludeoxyglucose F 18 Injection results to subsphenoidal EEG, MRI and/or surgical findings supported the concept that the degree of hypometabolism corresponds to areas of confirmed epileptogenic foci. The safety and effectiveness of Fludeoxyglucose F 18 Injection to distinguish idiopathic epileptogenic foci from tumors or other brain lesions that may cause seizures have not been established.

15 REFERENCES

1. Gallagher B.M., Ansari A., Atkins H., Casella V., Christman D.R., Fowler J.S., Ido T., Mac-Gregor R.R., Som P., Wan C.N., Wolf A.P., Kuhl D.E., and Reivich M. "Radiopharmaceuticals XXVII. ¹⁸F-labeled 2-deoxy-2-fluoro-d-glucose as a radiopharmaceutical for measuring regional myocardial glucose metabolism in vivo: tissue distribution and imaging studies in animals," *J Nucl Med*, 1977; 18, 990-6.
2. Jones S.C., Alavi, A., Christman D., Montanez, I., Wolf, A.P., and Reivich M. "The radiation dosimetry of 2 [F-18] fluoro-2-deoxy-D-glucose in man," *J Nucl Med*, 1982; 23, 613-617.
3. Kocher, D.C. "Radioactive Decay Tables: A handbook of decay data for application to radiation dosimetry and radiological assessments," 1981, DOE/TIC-1 1026, 89.
4. ICRP Publication 53, Volume 18, No. 1-4, 1987, pages 75-76.

16 HOW SUPPLIED/STORAGE AND DRUG HANDLING

Fludeoxyglucose F 18 Injection is supplied in a multi-dose, capped 30 mL and 50 mL glass vial containing between 0.740 to 7.40GBq/mL (20 to 200 mCi/mL), of no carrier added 2deoxy-2-[F 18] fluoro-D-glucose, at end of synthesis, in approximately 15 to 50 mL. The contents of each vial are sterile, pyrogen-free and preservative-free.

NDC 40028-511-30; 40028-511-50

Receipt, transfer, handling, possession, or use of this product is subject to the radioactive material regulations and licensing requirements of the U.S. Nuclear Regulatory Commission, Agreement States or Licensing States as appropriate.

Store the Fludeoxyglucose F 18 Injection vial upright in a lead shielded container at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Store and dispose of Fludeoxyglucose F 18 Injection in accordance with the regulations and a general license, or its equivalent, of an Agreement State or a Licensing State. The expiration date and time are provided on the container label. Use Fludeoxyglucose F 18 Injection within 12 hours from the EOS time.

17 PATIENT COUNSELING INFORMATION

- Instruct patients in procedures that increase renal clearance of radioactivity. Encourage patients to:
- drink water or other fluids (as tolerated) in the 4 hours before their PET study.
 - void as soon as the imaging study is completed and as often as possible thereafter for at least one hour.

Manufactured by: PETNET Solutions Inc.
810 Innovation Drive
Knoxville, TN 37932

Distributed by: PETNET Solutions Inc.
810 Innovation Drive
Knoxville, TN 37932

PETNET Solutions

.....
Siemens Healthineers Headquarters

Siemens Healthcare GmbH

Henkestr. 127

91052 Erlangen, Germany

Phone: +49 9131 84-0

[siemens.com/healthineers](https://www.siemens.com/healthineers)