# FDG PET/CT Features of Polysaccharide-Based Hemostatic Agent

## *Chronic Inflammatory Changes Can Mimic Metastatic Lesions*

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**Purpose:** To prevent hemorrhagic complications, hemostatic agents (HAs) have been widely used in recent years. The use of HAs can lead to false-positive results on postoperative imaging. There exists only 1 study in the literature evaluating these applications during surgical procedures. Therefore, we aimed to evaluate the postoperative imaging features of polysaccharide-based HAs in thoracic surgery patients who have had $^{18}$F-FDG PET/CT scans.

**Patients and Methods:** Two hundred nine consecutive patients who underwent thoracic surgery were enrolled in this study. A topical polysaccharide-based HA was applied to the surgical bed for all of the patients. The patients diagnosed with cancer were followed up with subsequent thoracic CT scans, and 42 of these patients were also imaged with $^{18}$F-FDG PET/CT, which then comprised the main study group. Due to suspicion of metastasis, 19/42 patients were reoperated or rebiopsied. The latest histopathological findings were accepted as criterion standard, and previous FDG PET/CT images were retrospectively reevaluated.

**Results:** Polysaccharide-based HAs that appear as amorphous basophilic material were identified in histopathological samples of 11/19 patients. Lymphocytes, plasma cells, and histiocytes, which formed foreign body reaction and/or foreign body granuloma, indicating the presence of chronic inflammation, were seen in all of the samples. $^{18}$F-FDG PET/CT showed increased FDG uptake in all of these lesions.

**Conclusions:** Despite the inconsistency of the literature, polysaccharide-based HAs can be demonstrated in human surgical specimens as amorphous basophilic materials even after a long time from the initial surgical procedure. These agents almost always cause chronic inflammatory changes. In addition, these agents may mimic "false-positive" findings on postoperative FDG PET/CT scans.

**Key Words:** FDG PET/CT, hemostatic agent, chronic inflammation, foreign body reaction, foreign body granuloma, false-positive assessment

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Intraoperative and postoperative bleeding is a life-threatening major complication of thoracic surgery that increases morbidity and mortality. To prevent hemorrhagic complications, topical hemostatic agents (HAs) have been widely used in the last decade during surgery. These agents can be categorized into 4 main groups: absorbable agents, biologically active agents, dual agents, and adhesives. Absorbable agents can be divided into 4 categories by their different physical origin: (1) polysaccharide-based, (2) gelatin-based, (3) collagen-based, and (4) cellulose-based.

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Polysaccharide-based absorbable HAs are among the most used ones in surgical practice. The safety of use of polysaccharide-based HAs has been evaluated by different studies, which showed that safer results would be obtained by these agents than the cellulose-based and gelatin-based ones.[1–4]

There are a limited number of studies investigating the effectiveness of polysaccharide-based HAs.[5–7] Therewithal, HAs can lead to some clinical complications such as inflammatory reactions or tumor-like mass lesions that have also been reported.[8–10] Oksuzoglu et al[8] recently published a case report that was considered having a false FDG PET-positive pulmonary nodular formation in favor of metastasis that was formed due to the use of polysaccharide-based HA. Another false-positive common iliac lymph node activity was reported by Fournet et al.[11] In accordance with these literature data, it can be asserted that the use of topical HAs during surgery can lead to false-positive results on postoperative imaging. Interestingly, there exists only one study in the literature evaluating these applications during surgical procedures in the abdomen and pelvis along with their radiologic appearances.[12]

Therefore, we here aimed to evaluate the postoperative imaging features of polysaccharide-based HAs in thoracic surgery patients who have had FDG PET/CT scans.

## PATIENTS AND METHODS

### Study Design and Patient Population

Over a period of 5 years (January 2016 to September 2021), a total of 209 consecutive patients who underwent thoracic surgery were enrolled in this retrospective study. A topical polysaccharide-based HA was applied to the surgical bed for all of the patients to prevent perioperative bleeding complications. Of these patients, 73 with benign postoperative histopathologic results were not followed up. Patients with diffuse pleural metastasis (n = 3) and who were diagnosed as mesothelioma (n = 14) were also excluded from the study. The remaining patients diagnosed with cancer (n = 119) were followed up with subsequent thoracic CT scans for a period of 25.5 ± 18 months. Forty-two of these patients were also imaged with $^{18}$F-FDG PET/CT at our institution, which then comprised the main study group. Due to suspicion of metastasis, 19 of 42 patients were reoperated or rebiopsied. The mean time between the first thoracic surgical procedure and the second surgical intervention or second biopsy was 12.5 ± 10.5 months in these patients. The histopathological findings of these last procedures were accepted as criterion standard, and previous FDG PET/CT images were reevaluated by 2 experienced nuclear medicine physicians by consensus. Remained subjects (23/42 patients) were followed up with subsequent thoracic CT and/or new $^{18}$F-FDG PET/CT scans for a period of 24 ± 18.5 months as mentioned earlier. Shrinking lesions were interpreted as benign if they showed lower FDG uptake in subsequent follow-up scans. Figure 1 shows a flow diagram of patient recruitment.

This study was performed with local institutional review board approval (dated November 2020; number 09.2020.1215).

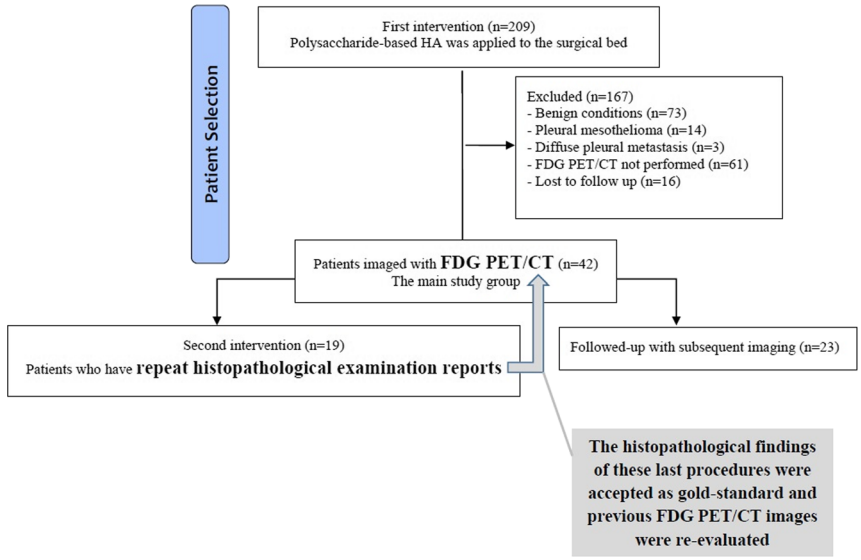


**FIGURE 1.** The patient flow diagram of the study.



## Histopathological Analysis

The pathological samples consisted of formalin-fixed paraffin-embedded tissue blocks of excisional and core needle biopsies and cell blocks of cytological material. The sections were derived from the blocks containing pathological samples and were cut at 3 μm thickness. One slide of each case was stained with hematoxylin-eosin. In addition, for each case, representative slides were stained with periodic acid–Schiff (PAS) and CD68 immunohistochemical stain. The primary mouse monoclonal anti-CD68 antibody clone Kp-1 was obtained from Cell Marque (Rocklin, CA) and used at a dilution of 1:100. Immunostaining was performed using the Ventana BenchMark ULTRA IHC/ISH automated staining system and ultraView Universal DAB Detection Kit (Ventana Medical Systems, Inc, Tucson, AZ). Strong cytoplasmic staining of histiocytes and giant cells was observed with CD68.

## $^{18}$F-FDG PET/CT Imaging Protocol

The patients fasted for a minimum of 6 hours and were hydrated with glucose-free water before the $^{18}$F-FDG PET/CT study. Patients' blood glucose levels were measured just before the injection of $^{18}$F-FDG. All patients were required to have <150 mg/dL of blood glucose level before injection. $^{18}$F-FDG (3.7 MBq/kg) was administered intravenously. Image acquisition was performed using an integrated PET/CT scanner (GE Discovery ST; GE Healthcare, Milwaukee, WI) approximately 60 minutes after $^{18}$F-FDG administration. Whole-body PET images and low-dose CT scan only for attenuation correction and anatomical orientation from skull base to midthigh were acquired. The acquired data were reconstructed using an iterative algorithm and transferred to Advantage Windows Workstation (Advantage Windows Server 4.5; GE Healthcare) for processing and interpretation.

## Statistical Analysis

Univariate descriptive statistics (mean, median, standard deviation [SD], and range) were calculated on SPSS (Statistical Package for Social Sciences) version 25.

# RESULTS

## Characteristics of the Patients

The characteristics of the study patients (n = 42) who were evaluated with $^{18}$F-FDG PET/CT are presented in Table 1. Ages ranged from 31 to 80 years; the median age was 64.5 years. The median follow-up was 20 months. Most were male (33/42, 79%), and they were mainly aged between 45 and 80 years. The imaging findings of $^{18}$F-FDG PET/CT were classified into 4 groups:

- newly developed lung nodules,
- imaging findings of lymph nodes,
- pleural thickening, and
- imaging findings of bronchial stumps.

## Results of the Patients Who Have Repeat Histopathological Examination

Polysaccharide-based absorbable HAs that appear as amorphous basophilic material with the same color but different shapes were identified in histopathological samples of 11 of 19 patients. Lymphocytes, plasma cells, and histiocytes, which formed foreign body reaction and/or foreign body granuloma, indicating the presence of chronic inflammation, were seen in all of the samples:

**TABLE 1.** The Patients' General Characteristics (n = 42)

| **Age** | **64 ± 11** |
|---|---|
| Sex (M/F) | 33/9 |
| Diagnosis | |
| Lung cancer | 32 |
| Adenocarcinoma | 20 |
| Squamous cell carcinoma | 10 |
| Large cell neuroendocrine carcinoma | 1 |
| Mucoepidermoid carcinoma | 1 |
| Non-Hodgkin lymphoma | 4 |
| Breast cancer | 2 |
| Sarcoma | 2 |
| Renal cell carcinoma | 1 |
| Colon adenocarcinoma | 1 |

M, male; F, female.

- Three samples were originated from lung parenchyma,
- Three samples were originated from lymph nodes,
- Four samples were originated from pleura, and
- One cytological specimen was obtained from bronchial lavage.

$^{18}$F-FDG PET/CT showed increased FDG uptake in all of these lesions (Fig. 2). The highest $SUV_{max}$ value was in a pleural thickening area, reaching 13.15. In addition, increased FDG uptake was observed at bronchial stumps in 4 patients, and one of them was evaluated with histopathological method.

For the remaining 8 of 19 cases, unrelated histopathological diagnosis/changes were reported such as malignancy, anthracosis, or atypical squamous metaplasia.

The details of the histopathological data and FDG PET/CT findings are summarized in Table 2.

### Results of the Patients Who Have Followed Up With Subsequent Imaging

The remaining cases (n = 23) were further evaluated with subsequent confirmatory imaging within an average of 24 months (range, 3 to 59 months). Twenty-one patients had undergone CT scans at least twice. In addition, 72 $^{18}$F-FDG PET/CT scans were performed as routine follow-up. Both studies were performed in 22 patients. To summarize the results briefly, our main findings are as follows:

- During follow-up, newly developed 34 lung nodules were detected in 8 patients. One of these nodules disappeared in follow-up and was interpreted as benign.
- All of the enlarged lymph nodes (n = 4) with higher FDG uptake were interpreted as metastatic.
- In 18 patients, $^{18}$F-FDG PET/CT showed multiple zones of hypermetabolic pleural thickening areas with a range of $SUV_{max}$ ranging from 1.0 to 4.95.
- In 9 patients, increased FDG uptake was found at bronchial stumps.

## DISCUSSION

To our knowledge, this is the first study to investigate the FDG PET/CT imaging features of polysaccharide-based HAs with histopathologic comparison in thoracic surgery patients. The results of this study showed that these agents can be demonstrated in pathological specimens as amorphous basophilic materials and can cause "false-positive" results on FDG PET/CT. Chronic inflammatory changes were also seen in all histologic samples.

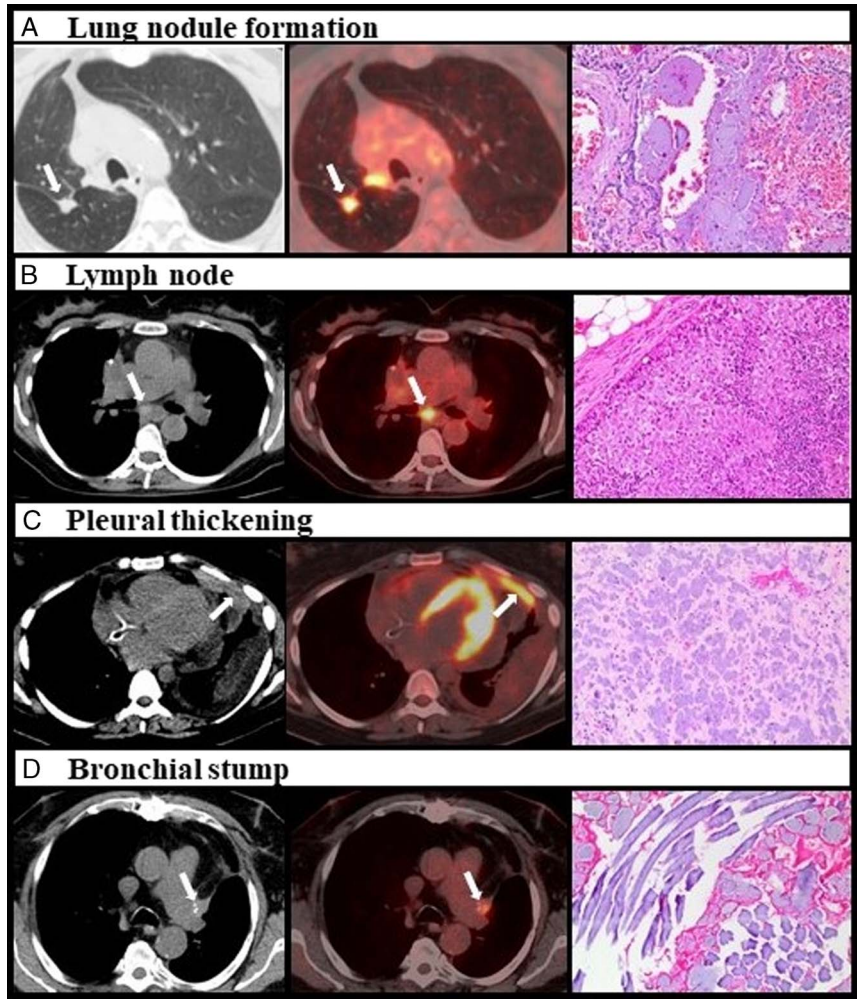


**FIGURE 2. A–D**, Axial CT (first column) and fused FDG PET/CT images (second column) depicted increased FDG uptake in related fields/tissues (arrows), respectively. Polysaccharide-based hemostatic agent manifested as amorphous basophilic materials in histopathologic specimens (third column), respectively, hematoxylin-eosin, ×20.

**TABLE 2.** The Details of the Histopathological Data and FDG PET/CT Findings (n = 19)

| | |
|---|---|
| Amorphous basophilic material | 11 of 19 Patients<br>3/11 ➔ Lung nodule samples<br>3/11 ➔ Lymph node samples<br>4/11 ➔ Pleural samples<br>1/11 ➔ Cytological sample |
| Foreign body reaction | 6 of 19 Patients<br>2/6 ➔ Lung nodule samples<br>3/6 ➔ Lymph node samples<br>1/6 ➔ Bronchial stump |
| Foreign body granuloma | 5 of 19 Patients<br>1/5 ➔ Lung nodule sample<br>4/5 ➔ Pleural samples |
| Hypermetabolic lung nodule formations | 16 Lung nodule formations (8/19 patients)<br>10/16 ➔ Inflammatory changes (3/8 patients) ($SUV_{max}$ range, 1.3–3.45)<br>6/16 ➔ Malignant changes (5/8 patients) |
| Hypermetabolic lymph nodes | 11 Lymph nodes in 7 of 19 patients<br>6/11 ➔ Inflammatory changes (3/7 patients) ($SUV_{max}$ range, 3.83–4.86)<br>5/11 ➔ Malignant changes (4/7 patients) |
| Hypermetabolic pleural thickening areas | 15 of 19 Patients ($SUV_{max}$ range, 1.0–13.15)<br>12/19 ➔ Local<br>3/19 ➔ Diffuse |
| Hypermetabolism at bronchial stumps | 5 of 19 Patients<br>4/5 ➔ Inflammatory changes ($SUV_{max}$ range, 2.89–9.36)<br>1/5 ➔ Malignant changes |



Polysaccharide-based HAs create a gel-like, adhesive mass after being applied to the bleeding site, and this structure acts as a sieve to concentrate platelets and clotting factors in the region and lead to clot formation.[13,14] They are then degraded by histaminases and almost completely absorbed from the implantation site within a time of approximately 24 to 48 hours.[5,15] In 2014, Bruckner et al[16] reported in a retrospective study that the application of topical polysaccharide-based HAs during cardiothoracic procedures resulted in a reduction in intraoperative hemostasis time, decrease in postoperative blood loss, and reduced need for blood product transfusion in the first 48 hours after surgery. It has also been noted recently that these agents are at least as effective as conventional methods in the management of nonvariceal upper gastrointestinal system bleeding.[7] Decrease in the lymphocele formation after kidney transplantation and reduced rates of postoperative hemorrhage after thyroid surgery were other positive outcomes.[5,6]

Perhaps the closest to our article is a recent study by Morani et al,[12] which focused on various types of topical tissue sealants and HAs used during surgical and percutaneous procedures in the abdomen and pelvis along. In their study, it has been reported that the normal appearance of these agents may mimic enlarged lymph nodes or retained foreign bodies. In our study, hypermetabolic pleural thickening areas were the most common imaging finding on FDG PET/CT scans but not reported in most cases. In addition, newly developed hypermetabolic "false-positive" lung nodules and mediastinal lymph nodes were also noticed and confirmed by immunohistochemical findings. Chronic inflammatory changes have been noticed in almost every histopathologic specimen with mild or moderate FDG uptake. Benign inflammatory $^{18}$F-FDG uptake (histopathologically confirmed) at one bronchial stump was another finding of this study.

In a systematic review of the literature, we identified some studies focusing on granuloma formation and foreign body reaction associated with the use of polysaccharide-based HAs.[1,3,4,16–22] In fact, although in these studies, it has been considered that there was no granuloma formation or foreign body reaction that was noted, in our study, contrary to the literature, foreign body

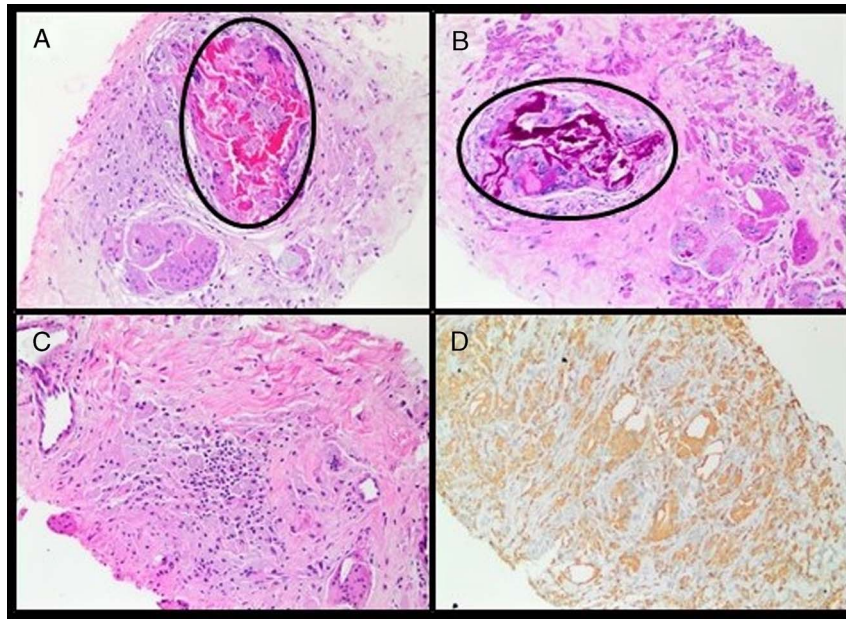


**FIGURE 3.** Foreign body type granulomas with amorphous basophilic material accumulation in histiocytes and giant cells, hematoxylin-eosin, ×20 (**A**). PAS positive amorphous material in the center of foreign body type granuloma and the cytoplasm of histiocytes and giant cells, PAS stain, ×20 (**B**). Histiocytic infiltration with cytoplasmic amorphous basophilic material and accompanying chronic inflammation with lymphocytes and plasma cells, hematoxylin-eosin, ×20 (**C**). Histiocytes and giants cells were positive for CD68 immunohistochemical stain, ×20 (**D**).

type granuloma formation was observed in pleura and lung parenchyma, in 5 samples (Fig. 3). Our findings suggested that these agents can be absorbed through the pleural surface and then they can migrate to the lung parenchyma either. Foreign body type granuloma formation is a distinctive pattern of chronic inflammation and response and an effort to restrict the exogenous agent that persists for longer periods in tissue. In our study, these materials were observed up to 24 months after the first thoracic surgical procedure. As mentioned earlier in our publication and together with the literature, there seems to be a relationship between which substance the HA contains and $^{18}$F-FDG uptake related to an inflammatory foreign body reaction developing against this agent (Fig. 3).[3,8,12,20,22]

$^{18}$F-FDG PET/CT is a pivotal imaging tool for thoracic malignancies and has been widely used to assess treatment response in a variety of malignancies such as lung cancer, thymic epithelial tumor, lymphoma, and esophageal cancer.[23–27] Although FDG uptake is related to the expression of the glucose transporter in malignant lesions, FDG can also accumulate in benign lesions and tissues affected by inflammatory processes. It is well established that activated inflammatory cells, such as activated granulocytes, lymphocytes, and macrophages overexpress glucose transporters, enhance glycolysis and therefore show increased FDG uptake.[28–31] Therefore, infective and inflammatory complications almost always cause problems in differentiating benign conditions from malignant lesions. Moreover, increased SUVs are not uncommon in acute or chronic inflammatory changes and not always indicative of a malignant process.[28,32] It is therefore crucial to avoid unnecessary biopsies or surgical procedures; false-positive results due to the use of HAs should be taken into consideration while interpreting postoperative FDG PET/CT imaging findings. The operative reports should be written with sufficient information in detail, describing which HA has been used and the application sites, to allow for correct interpretation of data.

The main limitations of our study include its retrospective and single-institutional design. The relatively small sample size is another limitation. Despite these limitations, the strongest aspect of this study is that it is the first publication that related agents have been shown with confirmatory histopathological evaluation in human surgical specimens even after 24 months from the application. Further large studies possibly with different protocols are warranted to better delineate to confirm our findings.

In conclusion, despite the inconsistency of the literature, polysaccharide-based HAs can be demonstrated in human surgical specimens as amorphous basophilic materials even after a long time from the initial surgical procedure. These agents almost always cause chronic inflammatory changes. In addition, these agents may mimic "false-positive" findings on postoperative FDG PET/CT scans. Therefore, to prevent the need for additional invasive procedures, the interpreting physicians should be informed about surgical procedure and used materials in detail while interpreting FDG PET/CT scans.



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