Impact of $^{68}$Ga-FAPI-04 PET/CT on Staging and Therapeutic Management in Patients With Digestive System Tumors

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**Purpose:** We aimed to determine the impact of fibroblast activation protein inhibitor (FAPI)–directed molecular imaging on staging and therapeutic management in patients affected with digestive system tumors when compared with guideline-compatible imaging (GCI).

**Patients and Methods:** Thirty-two patients with tumors of the digestive system were included: colon adenocarcinoma, 2/32 (6.3%); hepatocellular carcinoma (HCC), 6/32 (18.8%); pancreatic duct adenocarcinoma (PDAC), 6/32 (18.8%); and gastroenteropancreatic neuroendocrine neoplasms, 18/32 (56.3%). All patients underwent GCI and $^{68}$Ga-FAPI-04 PET/CT within median 4 days. Staging outcomes and subsequent treatment decisions were compared between GCI and $^{68}$Ga-FAPI-04 PET/CT.

**Results:** Compared with GCI, $^{68}$Ga-FAPI-04 PET/CT led to staging changes in 15/32 patients (46.9%). Among those, downstaging was recorded in 3/15 cases (20.0%) and upstaging in the remaining 12/15 patients (HCC, 4/12 [33.3%]; PDAC, 4/12 [33.3%]; neuroendocrine neoplasms, 3/12 [25%]; colon adenocarcinoma, 1/12 [8.3%]). Therapeutic management was impacted in 8/32 patients (25.0%), including 4 instances of major and 4 instances of minor therapeutic changes. The highest proportion of treatment modifications was observed in patients diagnosed with PDAC and HCC in 6/8 (75%).

**Conclusions:** In patients affected with digestive system tumors, $^{68}$Ga-FAPI-04 PET/CT resulted in staging changes in more than 46% and therapeutic modifications in 25% of the cases, in particular in patients with HCC and PDAC. In clinical routine, such findings may favor a more widespread adoption of FAP-directed imaging in those tumor types.

**Key Words:** $^{68}$Ga-FAPI, TNM, staging, fibroblast activation protein, therapeutic management, neuroendocrine neoplasm, HCC, PDAC, NET

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The incidence of cancers of the digestive system is steadily increasing, causing more than 25% of tumor-related deaths in 2020 among all oncological diagnoses.1–3 As imaging is an integral part of modern cancer management, accurate image-guided diagnostics play a key role for therapeutic decision-making,4 favorably leading to improved outcome.

For tumors of the digestive tract, current guidelines recommend conventional imaging (including CT or MRI) and various PET agents, such as $^{18}$F-FDG or $^{68}$Ga-DOTATOC.5–7 However, cirrhatic changes may significantly hamper lesion detection by CT/MRI, whereas increased background activity and uptake in normal organs on $^{18}$F-FDG PET may mask other sites of disease within the liver, spleen, or gut.8 Of note, cancer-associated fibroblasts (CAFs) have been identified to orchestrate development, angiogenesis, and tumor invasion in the majority of digestive tumors, thereby rendering CAFs as a suitable target for reliable assessment of the current status quo.9 Not surprisingly, head-to-head comparisons of $^{18}$F-FDG with the fibroblast activation protein inhibitor (FAPI)–targeting agent $^{68}$Ga-FAPI have already demonstrated an improved readout in widespread metastatic disease.10 Among others, Qin and coworkers11 also recently reported on a substantial portion of patients diagnosed with gastric and rectal cancer experiencing revision of diagnosis based on FAP-directed molecular imaging. The added clinical benefit of $^{68}$Ga-FAPI for individuals affected with other digestive tumors including hepatocellular carcinoma (HCC), pancreatic duct adenocarcinoma (PDAC), colon adenocarcinoma (CAC), or neuroendocrine neoplasm (NEN, including highly aggressive subtypes) has yet not been sufficiently explored. As such, in the present study, we aimed to investigate the clinical impact of $^{68}$Ga-FAPI-04 PET/CT on staging and therapeutic management in patients with those tumor types relative to guideline-compatible imaging (GCI).

**PATIENTS AND METHODS**

For the present retrospective single-center study, the following inclusion and exclusion criteria were used to retrieve patients from our clinical database.

Inclusion criteria were as follows: solid cancers of the digestive system, request by the referring treating physician to conduct PET/CT to aid in clinical decision making, and availability of concurrent GCI.

Exclusion criteria were patients who received any tumor-specific treatment between GCI and FAPI PET/CT.

Written informed consent was obtained from all patients. The need for further approval was waived by the local institutional review board due to the retrospective nature of this study (number 20210415 02). Parts of this cohort have been reported
previously,\textsuperscript{12,13} but without investigating effects on staging and therapeutic management.

### Imaging Procedure

\textsuperscript{68}Ga-FAPI-04 synthesis and labeling was performed as described in Lindner et al.\textsuperscript{14} A Siemens Biograph mCT 64 or 128 scanner (Siemens Healthineers, Erlangen, Germany) was used. We acquired whole-body scans approximately 1 hour after an injected activity of 149 MBq (median; range, 95–239 MBq). 3D mode (matrix 200 × 200) was used for image acquisition, with an acquisition time of 3 to 5 min/bed position. Correction of emission data and image reconstruction were also performed.\textsuperscript{12,13}

For GCI, patients affected with PDAC or HCC received multiphasic CT and/or multiphasic MRI. One individual with PDAC received noncontrast full-dose PET/CT due to severely impaired renal function (patient 3). For the present investigation, however, only the CT portion was evaluated, thereby following recommendations of current guidelines for PDAC imaging.\textsuperscript{5} Patients with CAC underwent monophasic CT.\textsuperscript{6} CT scans were performed as part of clinical routine on a Siemens Somatom Force, Somatom Definition AS, Biograph 64 or 128, Definition Edge, and Somatom Open scanners (Siemens Healthineers, Erlangen, Germany). For MRI, Siemens Magnetom Avanto fit, Magnetom Skyra, Magnetom Prisma fit, or Magnetom Espree scanners (Siemens Healthineers, Erlangen, Germany) were used. For NEN staging, individuals affected with low-grade (G1/G2) neuroendocrine tumors (NETs) received \textsuperscript{68}Ga-DOTATOC PET/CT, whereas patients with high-grade (G3) NET or poorly differentiated neuroendocrine carcinomas (NECs), as well as mixed neuroendocrine/nonneuroendocrine neoplasms (MiNENs), underwent \textsuperscript{18}F-FDG PET/CT for GCI, following current guidelines.

### TABLE 1. Patient Characteristics

| Patient | Age, y | Sex | Diagnosis | Indication | Previous Surgery | Previous Chemotherapy |
|---------|--------|-----|-----------|------------|------------------|-----------------------|
| 1       | 60     | M   | PDAC      | PD/recurrence | Left pancreatic resection | Gem + nab-Pacl  |
| 2       | 44     | M   | PDAC      | PD/recurrence | pp-Whipple | FOLFIRINOX; Gem + nab-Pacl; nal-IRI 5-FU/LV |
| 3       | 91     | F   | PDAC      | Primary staging | — | — |
| 4       | 45     | M   | PDAC      | PD/recurrence | Left pancreatic resection | FOLFIRINOX; Cisplatin/Etoposide |
| 5       | 62     | M   | PDAC      | Primary staging | — | — |
| 6       | 48     | M   | PDAC      | PD/recurrence | Whipple | Gem |
| 7       | 52     | F   | HCC       | PD/recurrence | Partial hepatectomy; thorax wall and pulmonary metastasis resection; RTx (thorax wall) | — |
| 8       | 64     | M   | HCC       | PD/recurrence | Partial hepatectomy | — |
| 9       | 64     | M   | HCC       | PD/recurrence | LTx; Pulmonary metastasis resection | — |
| 10      | 62     | M   | HCC       | PD/recurrence | Partial hepatectomy | Sorafenib, regorafenib, cabozantinib |
| 11      | 77     | F   | HCC       | PD/recurrence | Partial hepatectomy | — |
| 12      | 54     | F   | HCC       | PD/recurrence | Partial hepatectomy | — |
| 13      | 68     | F   | CAC       | Primary staging | — | — |
| 14      | 55     | M   | CAC       | PD/recurrence | Tumor debulking, peritoneectomy with HIPEC | FOLFOX; cetuximab |
| 15      | 64     | F   | NEN (GIT NET G2) | Primary staging | — | — |
| 16      | 75     | F   | NEN (GIT NET G2) | PD/recurrence | Small bowel resection | Everolimus; TACE |
| 17      | 58     | F   | NEN (GIT NET G2) | Primary staging | — | — |
| 18      | 89     | M   | NEN (pancreas NET G3) | Primary staging | — | — |
| 19      | 56     | M   | NEN (pancreas NET G3) | PD/recurrence | — | Cisplatin/etoposide |
| 20      | 38     | F   | NEN (pancreas NET G3) | PD/recurrence | pp-Whipple | — |
| 21      | 42     | M   | NEN (pancreas NET G3) | Primary staging | — | — |
| 22      | 79     | F   | NEN (pancreas NEC) | Primary staging | — | — |
| 23      | 66     | M   | NEN (pancreas NEC) | PD/recurrence | Pulmonary metastasis resection | Cisplatin |
| 24      | 63     | F   | NEN (GIT NEC) | PD/recurrence | Hemicolecotomy | — |
| 25      | 57     | M   | NEN (GIT NEC) | Primary staging | — | — |
| 26      | 60     | F   | NEN (GIT NEC) | PD/recurrence | Hemicolecotomy | Capcitabine; carboplatin/etoposide |
| 27      | 69     | M   | NEN (GIT NEC) | Primary staging | — | — |
| 28      | 68     | M   | NEN (GIT NEC) | Primary staging | — | — |
| 29      | 56     | M   | NEN (GIT MiNEN) | PD/recurrence | pp-Whipple | FOLFIRI; carboplatin/etoposide |
| 30      | 59     | F   | NEN (GIT MiNEN) | Primary staging | — | — |
| 31      | 53     | M   | NEN (GIT MiNEN) | PD/recurrence | Endoscopic local resection | Cisplatin/etoposide |
| 32      | 59     | F   | NEN (GIT MiNEN) | PD/recurrence | Hemicolecotomy | — |

Patients are sorted by diagnoses. For patients with neuroendocrine neoplasms (NEN), subjects are also categorized according to different histological subtypes reflecting increasing disease aggressiveness.

PD, progressive disease; pp-Whipple, pylorus-preserving Whipple procedure; RTx, radiation therapy; LTx, liver transplantation; HIPEC, hyperthermic intraperitoneal chemotherapy; FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan, oxaliplatin; Gem, gemcitabine; nap-Paclitaxel, albumin-bound paclitaxel; nal-IRI 5-FU/LV, liposomal irinotecan, 5-fluorouracil/leucovorin; FOLFOX, 5-fluorouracil, leucovorin, oxaliplatin; FOLFIRI, 5-fluorouracil, leucovorin, irinotecan; TACE, transarterial chemoembolization.

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guidelines and standard procedures. 7,15 68Ga-DOTATOC PET/CT was performed approximately 45 minutes after injection of 88 MBq (median; range, 85–99 MBq) and 18F-FDG PET/CT approximately 1 hour after injection of 227 MBq (median; range, 158–316 MBq). FDG PET imaging was performed after a minimum 6-hour fasting period, and blood glucose levels were checked before radiotracer injection. Siemens Biograph mCT (64 or 128, Siemens Healthineers, Erlangen, Germany) was used for whole-body (vertex to proximal thighs) scans with or without IV contrast (activated automatic tube current modulation; reference mAs, 35 mAs for low-dose scans.

### TABLE 2. Staging and Management Comparison Between Conventional Imaging and 68Ga-FAPI-04 PET/CT

| Patient | Diagnosis | Guideline-Appropriate Imaging Modalities and Staging | 68Ga-FAPI-04 PET-Based Staging | Additional Findings on 68Ga-FAPI-04 PET | Staging Change | Management Change |
|---------|------------|--------------------------------------------------|--------------------------------|----------------------------------------|----------------|-------------------|
| 1       | PDAC       | CT: T0 N0 M0                                     | T1 N0 M1 (PER)                   | Peritoneal carcinosis; local recurrence | Up             | Major             |
| 2       | PDAC       | CT: T0 N2 M1 (HEP)                               | T0 N2 M1 (HEP, OSS)              | Bone metastases                        | Up             | Minor             |
| 3       | PDAC       | CT: T4 N0 M1 (PER)                               | T4 N0 M1 (PER, OSS, HEP)         | Bone and liver metastases              | Up             | Minor             |
| 4       | PDAC       | CT: T0 N0 M1 (HEP, OSS)                          | T0 N0 M1 (HEP, OSS, LYM)         | Distant lymph node metastases          | Up             | —                 |
| 5       | PDAC       | CT/MRI: T3 N0 M0                                 | T3 N0 M0                         | —                                       | —              | —                 |
| 6       | PDAC       | CT: T3 N0 M0                                     | T3 N0 M0                         | —                                       | —              | —                 |
| 7*      | HCC        | CT/MRI: no evidence of tumor                      | B: multinodular hepatic           | Hepatic local recurrence (multinodular liver lesions) | Up             | Major             |
| 8*      | HCC        | CT/MRI: no evidence of tumor                      | A: oligodular hepatic            | Bifocal hepatic local recurrence       | Up             | Major             |
| 9*      | HCC        | CT/MRI: C: extrahepatic (LYM)                    | C: extrahepatic (LYM, OSS)       | Bone metastases                        | Up             | Minor             |
| 10*     | HCC        | CT: C: extrahepatic (PUL, SPLE, LYM)             | C: oligodular hepatic + Extrahepatic (PUL, SPLE, LYM) | Hepatic local recurrence | Up             | —                 |
| 11*     | HCC        | CT/MRI: C: extrahepatic (TISS)                   | C: extrahepatic (TISS)            | —                                       | —              | —                 |
| 12*     | HCC        | CT/MRI: B: multinodular                           | B: multinodular                   | —                                       | —              | —                 |
| 13      | CAC        | CT: Tx N2 M1 (LYM)                               | Tx N2 M1 (LYM)                   | Visible primary in transverse colon     | Up             | Major             |
| 14      | CAC        | CT: T0 N0 M0                                     | T0 N0 M0                         | —                                       | —              | —                 |
| 15      | GIT-NET G2 | SSTR-PET: T2 N1 M1 (HEP)                         | T2 N1 M1 (HEP)                   | —                                       | —              | —                 |
| 16      | GIT-NET G2 | SSTR-PET: T0 N0 M1 (HEP, PER)                    | T0 N0 M1 (PER, PER)              | —                                       | —              | —                 |
| 17      | GIT-NET G2 | SSTR-PET: Tx N2 M1 (HEP)                         | Tx N2 M1 (HEP)                   | —                                       | —              | —                 |
| 18      | P-NET G3   | FDG PET: T3 N0 M0                                | T3 N0 M1 (HEP)                   | Visible hepatic metastasis             | Up             | —                 |
| 19      | P-NET G3   | FDG PET: Tx N1 M1 (HEP, OSS, LYM)                | T2 N1 M1 (HEP, OSS, LYM)         | Visible pancreatic primary             | Up             | —                 |
| 20      | P-NET G3   | FDG PET: T0 N1 M1 (HEP)                          | T0 N0 M1 (HEP)                   | No lymphonodal metastases              | Down           | —                 |
| 21      | P-NET G3   | FDG PET: T2 N0 M1 (HEP)                          | T2 N0 M1 (HEP)                   | —                                       | —              | —                 |
| 22      | P-NEC      | FDG PET: Tx N0 M1 (HEP, OSS)                     | Tx N0 M1 (HEP, OSS)              | —                                       | —              | —                 |
| 23      | P-NEC      | FDG PET: Tx N0 M1 (LYM)                          | T2 N0 M1 (LYM)                   | Visible pancreatic primary             | Up             | —                 |
| 24      | GIT-NEC    | FDG PET: T0 N1 M1 (PER, PER, LYM)                | T0 N1 M1 (PER, LYM)              | No pulmonary lesion                    | Down           | —                 |
| 25      | GIT-NEC    | FDG PET: T4, N1, M1 (HEP, PUL, OSS)              | T4 N1 M1 (HEP, PUL)              | No osseous lesion                      | Down           | Minor             |
| 26      | GIT-NEC    | FDG PET: T0 N1 M1 (HEP, PUL)                     | T0 N1 M1 (HEP, PUL)              | —                                       | —              | —                 |
| 27      | GIT-NEC    | FDG PET: Tx N0 M0                                | Tx N0 M0                         | —                                       | —              | —                 |
| 28      | GIT-NEC    | FDG PET: Tx N1 M1 (OS, LYM)                      | Tx N1 M1 (OS, LYM)               | —                                       | —              | —                 |
| 29      | GIT-MiNEN  | FDG PET: T0 N0 M1 (HEP, OSS)                     | T0 N0 M1 (HEP, OSS)              | —                                       | —              | —                 |
| 30      | GIT-MiNEN  | FDG PET: Tx N2 M1 (HEP, PUL)                     | Tx N2 M1 (HEP, PUL)              | —                                       | —              | —                 |
| 31      | GIT-MiNEN  | FDG PET: T0 N0 M0                                | T0 N0 M0                         | —                                       | —              | —                 |
| 32      | GIT-MiNEN  | FDG PET: Tx N1 M1 (HEP, PER, LYM)                | Tx N1 M1 (HEP, PER, LYM)         | —                                       | —              | —                 |

*Upstaging and major changes are marked in bold, downstaging and minor changes in italic.
*Staging and management according to the BCLC strategy.

GIT-NET, gastrointestinal tract neuroendocrine tumor; P-NET, pancreatic neuroendocrine tumor; P-NEC, pancreatic neuroendocrine carcinoma; GIT-NEC, gastrointestinal tract neuroendocrine carcinoma; SSTR-PET, somatostatin receptor positron emission tomography; HEP, hepatic; OSS, osseous; PER, peritoneal; TISS, soft tissue; LYM, lymphatic; SPLE, splenic.
160 mAs for full-dose scans; tube voltage, 120 keV/100 keV (mCT 64/mCT 128); pitch, 1.4/0.8 (mCT 64/mCT 128); collimation, 64/128 × 0.6 mm collimation; rotation time, 0.5 seconds; reconstructed axial slice thickness, 3.0–5.0 mm), and PET images were reconstructed using standard parameters (3D mode; matrix, 200 × 200; iterations, 3; subsets, 24 [mCT 64]/21 [mCT 128]; Gaussian filtering, 2.0 mm).

Image Evaluation Including Changes in Staging and Therapeutic Management

Two board-certified radiologists reviewed GCI in a consensus setting in a randomized order, whereas 68Ga-FAPI-04 PET/CT imaging was assessed by one board-certified nuclear medicine physician and one board-certified radiologist in a similar fashion. Readers were aware of diagnosis and scan indication (primary staging, or recurrence/progressive disease), but otherwise blinded to patient data and further imaging data. Staging results based on either GCI or FAP-directed PET/CT were established for all patients, using the BCLC (Barcelona Clinic Liver Cancer) strategy for patients with HCC16 and the eighth edition of the TNM classification for all other tumors.17–21 In addition, a dual board-certified internal medicine physician and gastroenterologist proposed clinical management and oncologic treatment based on GCI findings and FAPI PET/CT findings, respectively. Staging changes, additional or discrepant findings on FAP-targeted molecular imaging, and resulting changes in oncologic management were recorded. Management changes triggered by molecular imaging were rated depending on the level of clinical impact. In this regard, minor changes were recorded if an already anticipated treatment regimen by the clinician was only modified based on PET results. If FAPI PET, however, led to another type or intent of treatment, those modifications were classified as major changes.

Statistical Analysis

Descriptive analyses for patient characteristics and tumor characteristics were performed. Mean ± standard deviation is reported for normally distributed variables as determined by the Shapiro-Wilk test. Otherwise, median and range are presented. GraphPad Prism Version 9.3.1 (GraphPad Prism Software, La Jolla, CA) was used.

RESULTS

Patient Cohort

In the present study, 32 patients were included. Median time between GCI and FAPI imaging was 4 days. The median age was 60 years (range, 38–91 years; female, 14/32 [43.8%]). Diagnoses were as follows: NEN of pancreatic or gastrointestinal origin, 18/32 (56.3%, with

FIGURE 1. MIP, CT, PET, and fused images of patient 1 with recurrent PDAC. Local peritoneal carcinosis at the prepyloric level (red arrow) and local recurrence after left pancreatic resection (green arrow) are visualized on 68Ga-FAPI-04 PET (middle) and PET/CT (bottom) but not evident on conventional CT (top). This prompted a major change in therapeutic management. The blue arrow on the MIP image indicates nonspecific uptake at the margin of a fluid collection after distal pancreatectomy.
primary in the pancreas in 6/18 (33.4%); PDAC, 6/32 (18.8%); HCC, 6/32 (18.8%); and CAC in the remaining, 2/32 (6.3%). Twelve of 32 patients (37.5%) underwent imaging procedures during their initial workup, whereas in the remaining 20/32 (62.5%), scans were performed due to suspected progressive disease or recurrence (Table 1).

68Ga-FAPI-04–Triggered Staging Changes in Nearly Half of the Subjects

Relative to GCI, 68Ga-FAPI-04 PET/CT triggered staging changes in 15/32 (46.9%). Among those, downstaging was recorded in 3/15 cases (20.0%) and upstaging in the remaining 12/15 patients (HCC, 4/12 [33.3%]; PDAC, 4/12 [33.3%]; NEN, 3/12 [25%]; CAC, 1/12 [8.3%]). Thus, per tumor entity, upstaging was mainly recorded in HCC, PDAC (4/6, 66.6% each), and in 3/6 (50%) dedifferentiated NEN of pancreatic origin (G3 NET/NEC; Table 2).

Among all 12 upstaged patients, the following additional findings on FAPI-directed molecular imaging were recorded: PET/CT identified recurrent HCC in 3/12 cases (25.0%). In another 3/12 cases (25.0%), the pancreatic primary tumor or local recurrence was evident on 68Ga-FAPI-04 PET/CT, but was not visualized on GCI (Figs. 1, 2). Also, in 1/12 cases (8.3%), FAP-targeted molecular imaging located the primary tumor in a patient with CAC. Furthermore, in the remaining 5/12 (41.7%) upstaged patients, additional disease sites in at least one of the following organ compartments were recorded, with one patient showing concomitant novel osseous and hepatic metastases: skeleton (3 cases), liver (2 cases), and distant lymph node involvement (1 case). In the 3 patients that were downstaged based on FAPI imaging results, no evidence of metastases was seen on 68Ga-FAPI-04 PET/CT, but was found on GCI in the following locations in 1 case each (33.3%, respectively): lung, liver, and regional lymph nodes.

68Ga-FAPI-04 Impacted Patient Management in 25% of the Patients

68Ga-FAPI-04 PET/CT had an impact on oncological management in 8/32 patients (25.0%), with major and minor changes in 4/8 cases (50.0%), respectively (Table 2). Overall, the highest proportion of treatment modifications was observed in patients diagnosed with PDAC and HCC in 6/8 (75%).

In detail, the following changes on a patient level were recorded: in patient 1 with recurrent PDAC, 68Ga-FAPI-04 PET/CT was able to identify local recurrence and additional peritoneal carcinosis (Fig. 1), triggering a major treatment change with initiation of systemic chemotherapy. In patient 7 with recurrent HCC, 68Ga-FAPI-04 PET/CT showed extensive bilobar, multinodular liver involvement, whereas no tumor was evident on GCI, also resulting in recommending an additional systemic treatment. Similarly, in patient 8 with conventionally occult recurrent HCC, 68Ga-FAPI-04 PET/CT revealed a bifocal local recurrence, resulting in a major treatment change to local ablation. In patient 13, no primary tumor for an adenocarcinoma of unknown origin with widespread lymphatic disease was visualized on GCI. Based on 68Ga-FAPI-04 PET/CT, the primary in the transverse colon was identified, and specific systemic treatment could be initiated (Fig. 3). Additional bone metastases were identified on 68Ga-FAPI-04 PET/CT in 3 patients (patients 2, 3, and 9). Thus, bisphosphonates were added to the patients’ treatment regimens, which was considered a minor change of an existing therapeutic concept. In 1 patient (patient 25), no evidence of bone metastases was seen on FAP-targeted molecular imaging, and thus no additional bisphosphonate therapy was recommended. Figure 4 provides a comprehensive overview of staging changes and impact on therapy triggered by FAP-directed molecular imaging.

![FIGURE 2. Fused images (outer columns) and MIP (inner columns) of 18F-FDG PET/CT (left), and 68Ga-FAPI-04 PET/CT (right) of patient 19 with high-grade (G3) neuroendocrine tumor of the pancreas. Lymph node metastases (upper row, blue arrows) are readily identifiable on both modalities. Liver (middle row, pink arrows) and bone metastases (lower row, red arrows), however, show more pronounced uptake on 68Ga-FAPI-04 PET/CT. The pancreatic primary (middle row, green arrows) is apparent only on 68Ga-FAPI-04 PET/CT.](image-url)
Staging and Therapeutic Management Impact Based on Reasons for Scan Request

Reasons for requesting $^{68}$Ga-FAPI-04 PET/CT were as follows: inconclusive GCI, 16/32 (50%); suspicious lesions on GCI, 11/32 (34.4%); and negative GCI, 5/32 (15.6%).

In the 12 patients with upstaging, 6 (50%) were scanned due to inconclusive GCI. In those 8 patients, in whom change in management was recorded, 3/8 (37.5%) were allocated to the inconclusive GCI group and 3/8 (37.5%) received PET/CT due to suspicious lesions on GCI.

DISCUSSION

This study demonstrated that, in patients with solid cancers of the digestive system, $^{68}$Ga-FAPI-04 PET/CT may be more sensitive than GCI, leading to TNM/BCLC-based upstaging, in particular in HCC and pancreatic tumors (including PDAC and pancreatic G3 NET/NEC). In addition, therapeutic management was altered by $^{68}$Ga-FAPI-04 PET/CT in 25%, supporting the notion that in vivo imaging of CAFs may provide relevant implications for clinical management among a broad spectrum of digestive tumors.

Our results are in line with other studies that have shown comparable diagnostic performance and impact on management of $^{68}$Ga-FAPI PET/CT, especially in stroma tumors such as colorectal or gastric cancer.$^{10,22-25}$ For HCC, a previous investigation comparing $^{18}$F-FDG and $^{68}$Ga-FAPI reported on a markedly increased sensitivity for the latter PET agent,$^{26}$ which may be due to favorable tumor-to-background ratios compared with $^{18}$F-FDG. In cirrhotic liver, detection of lesions by CT or MRI may be challenging, whereas high background activity and organ uptake on FDG may further mask other cancerous lesions.$^{27}$ In the present study, FAPI PET identified otherwise occult local recurrence in 3/6 patients (50.0%) with HCC, and additional liver metastases in 2 more patients with extrahepatic malignancies, thereby emphasizing the potential added value of FAPI-targeted imaging in patients with primary and secondary liver cancer. Moreover, in 1/6 patients (16.7%) with HCC, additional bone metastases were discovered after administration of $^{68}$Ga-FAPI. Overall, upstaging occurred in 4/6 (66.7%) patients with HCC, leading to treatment changes in 3/6 cases (50.0%). Thus, beyond assessing widespread disease, this radiotracer seems to have also implications on management in HCC, which favors a more widespread adoption of this PET agent in this tumor entity. Comparable to our findings, Röhrich et al$^{23}$ reported on staging changes in 52% of PDAC patients when compared with conventional CT. We also observed upstaging in 4/6 (66.7%) PDAC patients after FAPI-targeted molecular imaging, whereas 3/6 patients (50.0%) experienced a change in their treatment regimen. Taken together, our and previous findings may pave the way for future studies focusing on subjects with PDAC or HCC to further define the role of $^{68}$Ga-FAPI in those tumor entities.

FIGURE 3. MIP, contrast-enhanced conventional CT, PET, and fused images of patient 13 with an adenocarcinoma of initially unknown origin. MIP demonstrated widespread lymphatic disease (green arrows). On conventional CT (top), no primary tumor was identified. $^{68}$Ga-FAPI-04 PET (middle) and PET/CT (bottom), however, identified the primary tumor in the transverse colon (blue arrow, later confirmed by colonoscopy-derived specimen), which led to a major treatment change.
In the present study, we enrolled a relatively large cohort of patients affected with NEN. This cancer type can be separated into well-differentiated NET and poorly differentiated NEC, as well as MiNEN. Mostly developing in the gastrointestinal tract and pancreas, NENs are graded using Ki-67, with G2 NEN having a proliferation index of 3% to 20% (G3, >20%). To date, the number of NEN patients that underwent FAPI-directed PET is rather limited. For instance, a total of 7 subjects with NEN of unspecified origin were previously enrolled, confirming potentially high tracer uptake in tumor lesions, whereas one study comprised 13 subjects exclusively focusing on the liver, but not on the extrahepatic tumor burden. In addition, several case reports reporting on gastrointestinal NEN yielded favorable imaging results of FAPI-directed molecular imaging. As such, we included 18 patients with NEN of the digestive system and demonstrated that FAP-targeted molecular imaging is a promising diagnostic tool for staging purposes in these patients, with FAPI PET leading to different TNM stages in 6/18 cases (33.3%) when compared with 18F-FDG, in particular in pancreatic G3 NET/NEC (Table 2; Figs. 1, 2). Beyond an improved readout, those increased rate of findings on 68Ga-FAPI may also provide a rationale for targeted endoradiotherapy in those otherwise difficult-to-treat NEN subtypes of the pancreas, preferably in a theranostic approach using 90Y-labeled theranostic twins. Moreover, in the subgroup of patients affected with MiNEN, FAP-targeted molecular imaging revealed no additional findings compared with GCI. As such, in this extremely rare diagnosis in the subgroup of NEN patients, FAPI PET may provide only limited benefit for the treatment plan of such patients.

There are several limitations to this study. The relatively low number of patients may trigger future prospective studies. Nonetheless, we investigated one of the largest cohorts of digestive system tumors including HCC, PDAC, CAC, and NEN imaged with FAPI-targeted PET and observed relevant clinical changes in particular in HCC and tumors of pancreatic origin. The relevance of such an investigation may be further fueled by the fact that those tumor entities commonly spread toward the liver, where 18F-FDG can only provide limited information on organ-specific involvement. As such, the present findings may provide a rationale to design future clinical trials focusing on those tumors of the digestive system, which often present with liver-dominant disease.

CONCLUSIONS

Compared with GCI, findings on 68Ga-FAPI-04 PET/CT resulted in staging changes in nearly half of the subjects affected with digestive system tumors, in particular in HCC and pancreatic tumors (PDAC, G3 NET/NEC). FAPI-targeted molecular imaging also prompted therapeutic management modifications in 25% (again in HCC or PDAC), thereby favoring the more widespread adoption of FAP-targeted imaging in those tumor types.

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