Functional Imaging

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Contents

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Abstract

Positron Emission Tomography (PET) has been in clinical practice since early 1990s; however, widespread use was hampered due to non-availability of anatomical reference. In the late 1990s and early 2000s, with the advent of hybrid imaging, PET/computed tomography (CT), the oncological utilization has increased significantly. PET/CT has been shown to have high sensitivity and negative predictive value for the detection of tumors, with many studies reporting superior utility of PET/CT over conventional anatomical imaging such as CT, magnetic resonance imaging (MRI), and ultrasound. Despite limited literature regarding utilization of PET/CT in gall bladder and biliary tract cancer, the available literature studies provide evidence for the potential advantage of PET/CT in staging, restaging, and detecting recurrence of gallbladder and biliary tract cancer.

1 Overview of PET and PET/CT

1.1 History

Positron emission tomography (PET) has been in clinical use since early 1990s; however, widespread use was hampered due to non-availability of anatomical reference. In the late 1990s and early 2000s, with the advent of hybrid imaging, PET/CT, the oncological utilization has increased significantly. Hybrid imaging has been helpful in improving diagnostic certainty.

PET is based on coincidence detection, where two photons are released when a positron annihilates an electron. These photons travel at 180° to each other. A ring of detectors is present around the patient, collecting this information. This information is then, utilizing various software, transformed into images to be visually and qualitatively interpreted by detecting metabolic differences between malignant and benign processes.

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1.2 National Oncologic PET Registry

The Centers for Medicare and Medicaid Services (CMS) included the use of 18F-FDG PET/CT in their National Coverage Determination for several solid tumors, which was eventually reviewed to provide coverage for initial and subsequent treatment strategies of most cancer types. The National Oncologic PET Registry (NOPR) was then developed in 2006 in response to the CMS proposal to expand coverage for 18F-FDG PET/CT to include cancers and indications not currently eligible for Medicare reimbursement. For these cancers, the PET/CT scan may be obtained under the coverage of an evidence-based development program, provided that the referring physician and PET provider submit data to a clinical registry assessing the impact of PET on patient management.

To date, over 150,000 patients have undergone 18F-FDG PET scans under the NOPR program, and, due to the documented value of PET in oncologic patient management, approximately 30 % of patients would have had a different management strategy based on PET/CT scan. In 2008, CMS was asked to reconsider its coverage policy for PET. In 2009, CMS released a decision memo for FDG-PET for solid tumors which included expanded coverage as per the results of the NOPR.

2 PET/CT Imaging Technique

PET provides whole-body three-dimensional images of metabolic processes of cells and tissue in the body by detecting gamma rays emitted by positron-emitting radionuclides [1]. Various radiotracers are available with the ability to measure cell metabolism, hypoxia, proliferation, angiogenesis, and apoptosis [2]. 2-deoxy-2-[18F]fluoro-D-glucose (18F-FDG) is the most frequently used radiopharmaceutical in oncologic PET/CT imaging [3]. Since tumor cells typically display increased metabolism [4], 18F-FDG accumulates to a greater degree in malignant tissue when compared to benign processes. As such, lesions may be identified and differentiated from normal tissue by various visual and quantitative processes that measure the degree of FDG uptake. However, a few tumors exhibit low FDG avidity due to their small size and a different metabolic profile. As such, these tumors (typically less than 10 mm) may be missed by functional PET imaging, leading to false-negative readings [2]. Furthermore, FDG is a non-specific tumor tracer as many have reported increased uptake in benign processes such as inflammation, infection, and abscesses [5]. 18F-FDG uptake may also be increased following radiotherapy and/or chemotherapy due to the body's own defense mechanisms, leading to an increased chance of false-positive images. This is because tissues exposed to therapy may exhibit benign reactive changes that are FDG-avid [2]. Nonetheless, research is ongoing regarding the optimal timing of functional PET imaging after therapy, the use of tumor-specific radiotracers, and the development of software that increases image resolution.

2.1 18-Fluorine Fluorodeoxyglucose

As mentioned previously, ^{18}F-FDG is the most commonly used radiotracer. Once the radiotracer is injected into the patient's bloodstream, it will lead to phosphorylation by hexokinase to 2-deoxy-2[^{18}F]fluoro-D-glucose-6-phosphate [3]. The tracer will then be distributed throughout the body with a short physical half-life of approximately 110 min [3]. Native glucose will undergo further metabolism, while ^{18}F-FDG will accumulate over time in most malignant cells, allowing for the differentiation between benign and malignant processes after, ideally, 60 min from when the radiotracer was injected [3].

The technique of measuring glucose utilization was first applied to mapping local cerebral glucose metabolism, in vivo, in humans [6]. Preclinical studies then suggested the use of ^{18}F-FDG for tumor metabolism in line with Warburg's observation of increased glucose uptake by malignant cells [6]. The value of ^{18}F-FDG for oncological management has been demonstrated in localization of the primary tumor, detection of local and distant metastasis, evaluation of response to therapy, and detection of residual disease and recurrence [3].

2.2 Quantification of Tumor Glucose Metabolism

To quantify the difference between normal glucose metabolism and that of malignant cells, standardized uptake value (SUV) is typically utilized [7]. SUV is a semi-quantitative method providing the radioactivity concentration from the region of interest (ROI), compared to uptake in the whole body. The SUV may be normalized to body mass, lean body mass, or body surface area [8]. SUVs based on body weight may vary greatly from one patient to the next; for example, the SUV of a heavy-weighted patient may be twice that of an average-weighted patient [9]. SUV corrected for lean body mass (SUL) and body surface area, however, is less dependent on body weight [9]. As such, SUL is more widely used, especially when monitoring response to therapy where the patient's weight may change significantly due to treatment. Various methods of standardizing quantitative assessment have been proposed, most recent being PET

Table 1 Diagnosis of the primary tumor in gallbladder and cholangiocarcinoma by PET/CT: comparison with conventional imaging

Study	Type	No. of patients	PET					Conventional imaging				
			Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Lee et al. [10]	P	99	84	70	93	48	82	90	71	94	60	87
Rodriguez et al. [11]	P	16	80	82	67	90	–	–	–	–	–	–
Petrowsky et al. [12]	P	61	100	33	90	6	53	71	33	90	7	56
Yamada et al. [13]	R	14	69	–	90	–	64	–	–	–	–	–

R retrospective study, *P* prospective study, *PET* positron emission tomography *or* fused PET/CT, conventional imaging includes contrast-enhanced CT and MDCT, *PPV* positive predictive value, *NPV* negative predictive value

response criteria in solid tumors (PERCIST) 1.0. It is along the lines of RECIST (Response Evaluation Criteria in Solid Tumors [8]).

3 Diagnostic Functional Imaging of Gallbladder and Biliary Tract Cancer

PET/CT has been shown to have high sensitivity and negative predictive value for the detection of tumors, with many studies reporting superior utility of PET/CT over conventional anatomical imaging such as CT, MRI, and ultrasound [5]. The role of PET/CT has been studied in various oncologic diseases for staging, evaluating treatment response, restaging, and follow-up [5]. However, limited data are available for the role of PET/CT in gallbladder and biliary tract cancers due to the low prevalence of these cancers and poor prognosis associated with them. Nonetheless, the available literature provides evidence for the potential advantage of PET/CT in staging, restaging, and detecting recurrence of gallbladder and biliary tract cancer.

4 Utilizing 18F-FDG PET/CT for Initial Treatment Strategy in Gallbladder Cancer

4.1 Staging

Patients with gallbladder carcinoma (GBC) typically present in advanced stages of the disease, rendering the staging process a crucial element to successful treatment planning early during the course of treatment. Very few studies have examined the role of PET/CT specific to GBC, but initial studies pooling the efficacy of PET/CT in both gallbladder and cholangiocarcinoma show promising results when compared to conventional imaging [such as contrast-enhanced CT (ceCT) and Multidetector Computed Tomography (MDCT)]. Sensitivity of PET/CT for the detection of the primary tumor ranges from 80 to 90 % [10–12] (see Table 1), allowing PET/CT to accurately differentiate between malignancy and benign conditions such as chronic cholecystitis and biliary colic, especially in cases of equivocal conventional imaging.

In addition to the importance of accurately localizing the primary tumor, the detection of regional and distant metastasis is crucial to the determination of initial treatment strategies. Lymph node involvement and presence of metastatic lesions may preclude surgical resection. With respect to the detection of regional lymph nodes, PET/CT does not seem to offer a significant advantage over conventional imaging with reported sensitivities ranging from 12–82 to 24–80 % for PET/CT and conventional imaging, respectively [10, 12] (see Table 2). There is a clear and significant advantage, however, of PET/CT for the detection of suspected and unsuspected distant lesions, with reported sensitivities ranging from 95–100 to 25–63 % for PET/CT and conventional imaging, respectively [10, 12] (see Table 3).

As a result of staging by PET/CT, treatment plans that were based on previous conventional staging were modified in up to 17 % of patients, whereby the detection of unsuspected metastasis by PET/CT led to non-surgical treatment, sparing unnecessary resection in patients deemed resectable following conventional work-up [10, 12] (see Figs. 1, 2, 3).

Much more research is warranted before definitive conclusions can be made; however, although limited, the data depict superiority of PET/CT for the staging of gallbladder cancer, especially in cases of equivocal conventional imaging, for evaluating metastatic disease, and for deciding on the initial treatment strategy.

4.2 Restaging

Very little data are available in the restaging setting, as such; the utility of PET/CT cannot be evaluated to a great extent. One prospective study compared PET/CT with MDCT for evaluating residual disease in patients with incidental gallbladder cancer [14]. Twenty-four patients with incidental gallbladder cancer who were suitable for

Table 2 Detection of nodal metastasis in gallbladder and cholangiocarcinoma by PET/CT: comparison with conventional imaging

Study	Type	No. of patients	PET					Conventional imaging				
			Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Lee et al. [10]	P	99	82	95	94	85	89	80	79	78	81	79
Petrowsky et al. [12]	P	61	12	96	67	64	64	24	86	50	65	62

P prospective study, *PET* positron emission tomography *or* fused PET/CT, conventional imaging includes contrast-enhanced CT and MDCT, *PPV* positive predictive value, *NPV* negative predictive value

Table 3 Detection of distant metastasis in gallbladder and cholangiocarcinoma by PET/CT: comparison with conventional imaging in prospective studies

Study	Type	No. of patients	PET					Conventional imaging				
			Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Lee et al. [10]	P	99	95	95	86	98	95	63	94	75	89	87
Petrowsky et al. [12]	P	61	100	100	100	100	100	25	100	100	85	85

P prospective study, *PET* positron emission tomography *or* fused PET/CT, conventional imaging includes contrast-enhanced T and MDCT, *PPV* positive predictive value, *NPV* negative predictive value

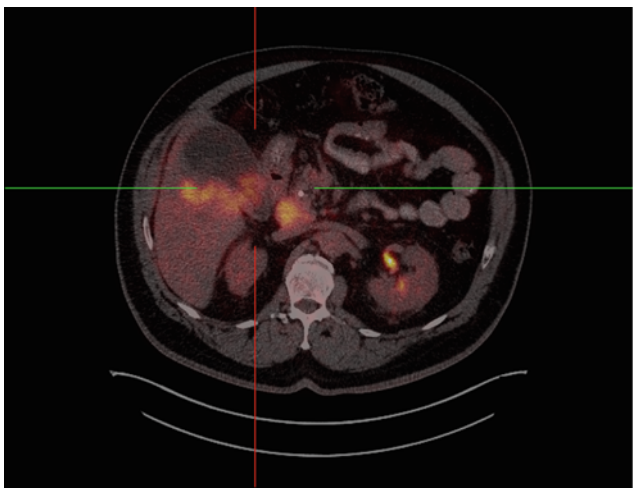

Fig. 1 54 year-old male with a newly found gallbladder mass. Axial fused staging 18F-FDG PET/CT image demonstrates intensely FDG-avid gallbladder wall thickening involving the posterior wall (SUV-max 10.1) and the hepatic parenchyma

surgery were recruited for the study [14]. For detecting residual disease, the authors reported a sensitivity and positive predictive value (PPV) of 28.5 and 20 % for PET/CT and 42.8 % each for MDCT, respectively [14]. Despite the low values, PET/CT was able to detect occult metastatic and loco-regional disease missed on MDCT, emphasizing the importance of using multimodality imaging in a complementary fashion as concluded by the authors as well [14].

5 Utilizing 18F-FDG PET/CT for Initial Treatment Strategy in Extra-Hepatic Cholangiocarcinoma

5.1 Staging

Similar to gallbladder cancer, malignancies of the biliary tract are also rare and have poor prognosis. There have been more studies, however, evaluating the role of PET/CT in biliary tract cancer, with the greatest advantages reported to be in detecting metastatic disease and selecting candidates for surgery [15]. Preoperative imaging is, thus, an integral part of initial assessment.

With respect to staging of the primary tumor, PET/CT seems to have limited or no clear advantage over conventional imaging techniques such as CT and MRI. This may be due to the overlap in FDG uptake between biliary tract malignancies and benign inflammatory lesions, especially in patients with primary sclerosing cholangitis (see Table 4).

The detection of metastatic lymph nodes by PET/CT has been reported to be limited; nonetheless, the sensitivity is significantly higher than that of conventional imaging, with sensitivity measures ranging from 37–76 to 33–60 % for PET/CT and CT, respectively [18, 20, 21] (see Table 5). As is the case in gallbladder cancer, the role of PET/CT in metastatic staging is undisputed, with many studies reporting significant advantage of PET/CT for detecting unsuspected metastatic disease (see Table 6).

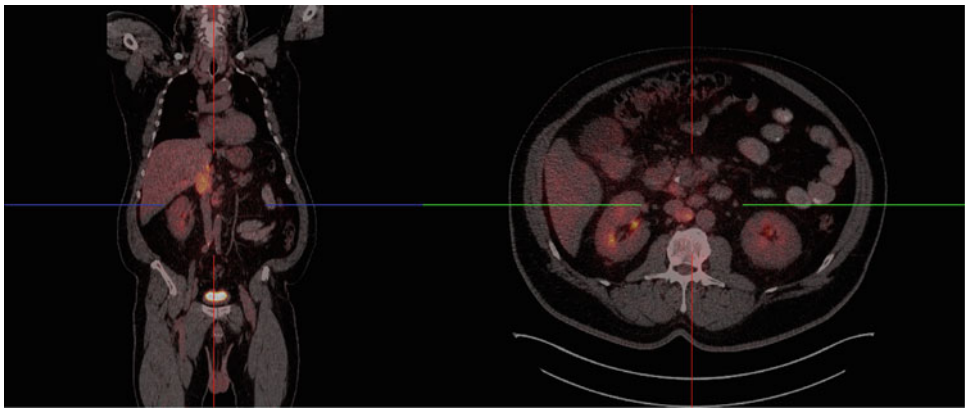

Fig. 2 Coronal (*left*) and axial (*right*) fused PET/CT images demonstrate FDG-avid lymphadenopathy involving the aortocaval nodes with the highest SUVmax of 6.6

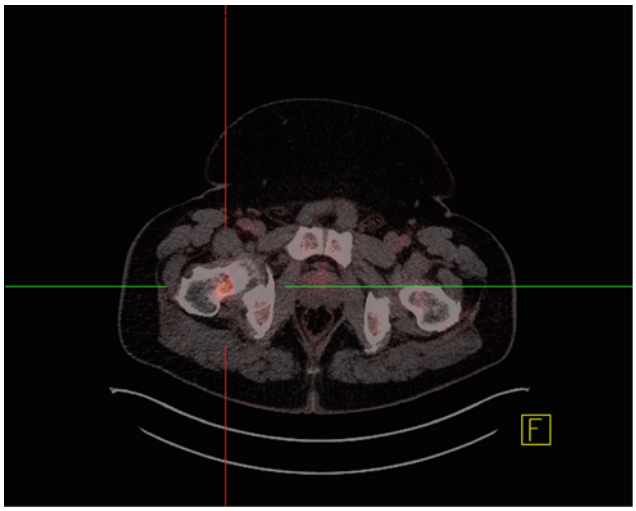

Fig. 3 Intense focal FDG uptake is noted in a lucent lesion involving the right femoral neck and is highly suspicious for malignant involvement with a SUVmax of 7.2

Moreover, due to the limitations of anatomical imaging, additional preoperative information provided by functional PET/CT may lead to a change in management in up to 16 % of patients [18], typically by detecting metastasis not seen on conventional imaging and consequently changing the patient's status from resectable to unresectable. Interestingly, one study also reported that while there was only a trend toward higher SUVs being associated with malignancy compared to benign biliary disease, the SUV of the primary tumor was significantly higher in patients with metastasis than in those without [20]; these results imply that resectability may be quantified, although more prospective trials are needed to evaluate this possibility.

In summary, it seems that the role of PET/CT in staging gallbladder and biliary tract cancers offers the greatest advantage in detecting metastatic disease and subsequently influencing patient management and treatment planning; much more research is needed, however, to determine the utility of PET/CT in primary and nodal staging.

6 Utilizing 18F-FDG PET/CT for the Detection of Recurrence in Gallbladder and Biliary Tract Cancers

Curative surgical resection is the ultimate goal of treatment for patients with gallbladder and biliary tract cancers; however, recurrence rates are still high even with resection [22]. The limited data available are heterogeneous, with some studies reporting superiority of PET/CT over conventional imaging for the detection of recurrence and others reporting no significant differences between the imaging modalities (see Table 7). However, most studies have recruited a small number of patients and the lack of statistical significance may be due to the small sample sizes. Furthermore, PET/CT findings, in light of clinical suspicion of recurrence, were reported to change subsequent treatment management in up to 20 % of patients [23] (see Fig. 4).

7 Future Direction and Conclusion

With PET/CT's introduction to clinical practice almost two decades ago, much data have accumulated regarding its utility in various oncologic diseases. Current research studies, however, have begun to search for alternate PET radiotracers that are tumor specific, unlike FDG. While this field of study has yet to target gallbladder and biliary tract cancers, several non-FDG radiotracers have been proposed to be useful in several other types of cancer. For example, angiogenesis, a process critical to tumor growth and survival, may be visualized by radiolabeled arginine–glycine–aspartic acid (RGD) peptides [27]. Apoptosis, which has been linked to unsuccessful therapy, may be quantified by

Table 4 Detection of primary cholangiocarcinoma tumor by 18F-FDG PET/CT

Study	Type	No. of patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Alkhawaldeh et al. [16]	R	65	94	83	94	83	91
Corvera et al. [17]	P	93	69	67	–	–	–
Kim et al. [18]	P	123	81	79	95	44	81
Li et al. [19]	P	17	59	–	100	0	–
Ruys et al. [20]	R	30	88	0	85	0	77
Yamada et al. [13]	R	20	84	–	94	–	80

R retrospective study, *P* prospective study, *PET* positron emission tomography *or* fused PET/CT, *PPV* positive predictive value, *NPV* negative predictive value

Table 5 Detection of nodal metastasis in cholangiocarcinoma by PET/CT: comparison with CT

Study	Type	No. of patients	PET					Conventional imaging				
			Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Corvera et al. [17]	P	93	93	86	–	–	–	–	–	–	–	–
Kim et al. [18]	P	123	32	88	43	82	76	47	65	27	82	61
Kobayashi et al. [21]	R	36	37	97	86	72	87	49	81	75	36	87
Li et al. [19]	P	17	42	80	39	36	–	–	–	–	–	–
Ruys et al. [20]	R	30	67	67	40	86	67	33	67	–	–	–

R retrospective study, *P* prospective study, *PET* positron emission tomography *or* fused PET/CT, *CT* computed tomography, *PPV* positive predictive value, *NPV* negative predictive value

Table 6 Detection of distant metastasis in cholangiocarcinoma by 18F-FDG PET/CT

Study	Type	No. of patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Corvera et al. [17]	P	93	93	86	–	–	–
Kim et al. [18]	P	123	58	93	54	94	88
Li et al. [19]	P	17	56	88	83	64	–
Ruys et al. [20]	R	30	33	96	66	85	83

R retrospective study, *P* prospective study, *PET* positron emission tomography *or* fused PET/CT, *PPV* positive predictive value, *NPV* negative predictive value

Table 7 Detection of recurrent disease by PET/CT: comparison with conventional imaging

Study	Type	No. of patients	PET					Conventional imaging				
			Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Kumar et al. [24]	R	49	94	100	100	89	96	88	50	78	67	75
Corvera et al. [17]	P	33	89	100	–	–	–	–	–	–	–	–
Jadvar et al. [25]	R	24	94	100	–	–	–	82	43	–	–	–
Kitajima et al. [23]	R	50	86	91			88	–	–	–	–	–
Lee et al. [26]	R	50	88	69	86	73	82	76	44	74	47	66

R retrospective study; *P* prospective study; *PET* positron emission tomography *or* fused PET/CT; conventional imaging includes computed tomography, magnetic resonance imaging, and MDCT; *PPV* positive predictive value; *NPV* negative predictive value

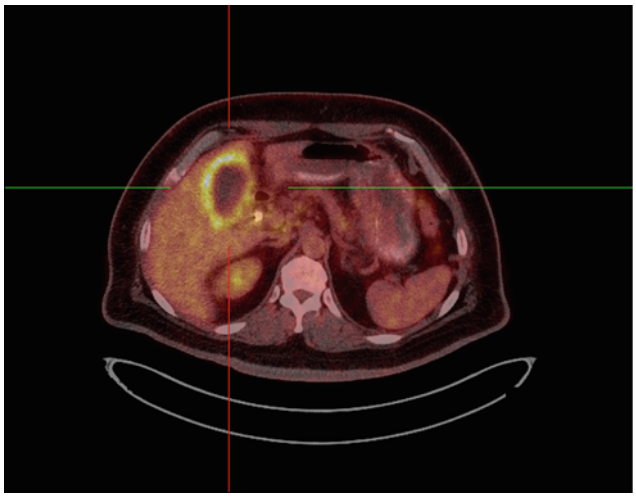

Fig. 4 54 year-old male with a history of cholangiocarcinoma with liver metastases. PET/CT scan was indicated for the evaluation of residual disease following completion of chemotherapy. Fused axial 18F-FDG PET/CT image demonstrates intensely FDG-avid thickening noted along the gallbladder with the highest SUVmax of 9.7. The wall thickening measuring up to 1 cm is consistent with persistent disease presence

^{18}F-Annexin V [27], allowing for the possibility of early identification of non-responders and changing their treatment accordingly. Tumors that exhibit hypoxia are also associated with chemoresistance and poor response to therapy, and 18-fluoride-fluoromisonidazole (^{18}F-FMISO) is currently the most widely studied radiotracer for measuring hypoxia [27]. Finally, proliferation, one of the biological hallmarks of cancer, may be imaged by 3-deoxy-3-18-fluoride-fluorothymidine (^{18}F-FLT) [27].

Recent research is also focusing on advanced software and techniques for optimized anatomical and functional imaging. The main area of interest is currently in fused PET/MR imaging. Several aspects may be considered when analyzing the utility of PET/MR. First, since PET and CT images are not acquired simultaneously, PET/CT imaging still faces the issue of misregistration, leading to reportedly up to 10 % of error in SUV calculations [28]. This is especially important in abdominal imaging where breathing and motion artifacts are a concern. More accurate attenuation correction may be achieved by using simultaneous and hybrid PET/MR scanners, eliminating the issue of misregistration. Second, due to the superior soft tissue contrast of MRI, fused PET/MR will benefit from increased accuracy of tumor and nodal localization. Third, the combination of quantitative MRI biomarkers and PET radiotracers may significantly improve the sensitivity, specificity, and accuracy of tumor detection and response to therapy. These concepts and advances in technology, however, have yet to be studied in a large pool of cancers, including gallbladder and biliary tract cancers.

To conclude, the use of ^{18}F-FDG PET/CT in gallbladder and biliary tract cancers is much less studied in comparison with more common malignancies, for example, lung and breast cancers. This is due to the rare nature of the disease, as well as the poor prognosis associated with it. However, despite the limited data, ^{18}F-FDG PET/CT seems to offer an advantage over conventional imaging for the detection of metastatic disease, recurrence, and subsequently changing management in a number of patients. As such, the use of FDG/non-FDG PET/CT and, subsequently, PET/MR for the management of gallbladder and biliary tract cancers should be assessed to a much greater degree in current clinical practice, allowing physicians a better anatomical and functional understanding of the patient's extent of disease.

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