Review Article

Diagnostic Challenges of Kidney Cancer: A Systematic Review of the Role of Positron Emission Tomography-Computerized Tomography

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Abbreviations and Acronyms

CAIX = carbonic anhydrase IX
CT = computerized tomography
E_{max} = energy output
FDG = fluorodeoxyglucose
FLT = fluorothymidine
MRI = magnetic resonance imaging
PET = positron emission tomography
RCC = renal cell carcinoma
RPh = radiopharmaceutical
SUV = standardized uptake value
SUV_{max} = maximum standardized uptake value
TKI = tyrosine kinase inhibitor
TLG = total lesion glycolysis

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Purpose: Positron emission tomography-computerized tomography is a leading imaging modality for many types of solid tumors. The ability to characterize molecular processes noninvasively during a relatively fast whole-body scan is the major advantage of this technology. We reviewed the literature in an attempt to clarify the usefulness of positron emission tomography-computerized tomography in patients with a renal mass.

Materials and Methods: We searched PubMed® for articles published from 2004 through September 2015 using the keywords "renal," "kidney," "mass," "tumor," "cancer," and "PET/CT."

Results: A total of 158 relevant articles were included in the review. Most diagnostic studies used ^{18}F-fluorodeoxyglucose, a marker of glucose metabolism, as the radiotracer. The results were substandard, with sensitivity rates in the range of 31.5% to 77% for diagnosis of renal cell carcinomas. There were higher success rates for diagnosis of clear cell carcinomas. Carbonic anhydrase IX is an enzyme expressed in 95% of clear cell carcinomas but not in normal renal tissue or in benign or nonclear cell malignancies. A chimeric mouse-human antibody to carbonic anhydrase IX labeled with ^{124}I-girentuximab was demonstrated to diagnose clear cell tumors with sensitivity of 86.2% and specificity of 85.9%. For diagnosis of metastases positron emission tomography-computerized tomography with ^{18}F-fluorodeoxyglucose was observed to be more accurate than computerized tomography alone (94% vs 89%). Studies with other tracers also reveal encouraging results. Positron emission tomography-computerized tomography holds great promise in predicting prognosis and response to tyrosine kinase inhibitors. Current tyrosine kinase inhibitor treatments usually induce only mild lesion shrinkage. Thus, assessment of response based on changes in size of metastases is insufficient. Low ^{18}F-fluorodeoxyglucose uptake before treatment and decreased uptake after 2 cycles of treatment are associated with better survival. Using labeled medications as radiotracers before actual treatment may assist in selection of the most effective medication for a specific patient.

Conclusions: Positron emission tomography-computerized tomography with ^{18}F-fluorodeoxyglucose currently has lower sensitivity compared to enhanced computerized tomography for diagnosis of primary renal masses but better sensitivity for diagnosis of metastases. Predicting and monitoring response to targeted therapy could direct the clinician toward drug selection or modification during therapy. The possibility of treating patients with advanced renal cell carcinoma with ^{124}I-girentuximab attached to ^{177}Lu, a strong β-emitter, is investigated.

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Key Words: diagnosis, computer-assisted; kidney neoplasms; positron-emission tomography; tomography, x-ray computed

THE finding of a solid renal mass raises several diagnostic challenges. What is the diagnosis? If the mass is malignant, is it clear cell carcinoma or a less aggressive form of kidney cancer? Is the disease localized or is there systemic spread? Is it possible to predict prognosis and response to systemic treatment if the renal cancer is advanced?

Ultrasonography, contrast enhanced CT and MRI are highly sensitive tools for diagnosis of solid renal masses.[1] CT and MRI are also the preferred modalities for evaluation of local and distant spread of tumor. Most patients with renal tumors and no evidence of metastases are referred to surgery as the next step, provided they have reasonable life expectancy and low operative risk. Pathological evaluation of the specimen can then be used to guide further treatment and followup.

However, in many instances the situation is not so clear. The presence of atypical masses with cystic or infiltrative components may lead to inclusion of a benign mass or nonrenal cell tumor in the differential diagnosis. Additionally it is desirable at times to avoid surgery if the tumor does not pose an immediate risk to life or the patient has a significant operative risk. In these situations a preoperative histological diagnosis can now be reliably obtained by percutaneous biopsy of the renal mass.[2] When even percutaneous biopsy is risky for the patient or is technically difficult, metabolic evaluation of the enhancing mass can potentially characterize the lesion. Fluorodeoxyglucose PET-CT has relatively high sensitivity for detection of metastases when determination of the presence and extent of metastatic disease with CT and MRI is inconclusive due to the presence of atypical or marginal findings in the abdomen and the chest.

Predicting and monitoring disease progression is another challenge that is unmet by CT and MRI. Since targeted therapy usually induces only mild lesion shrinkage, assessment of response according to RECIST (Response Evaluation Criteria in Solid Tumors) may be misleading.[3,4] Several TKI therapies are now available. Deciding which one should be prescribed first is based on empirical data and not on the metabolic profile of the patient. Furthermore, deciding when to stop therapy and when to convert to a different TKI is another difficult decision that could be assisted by metabolic evaluation.

PET-CT is a leading imaging modality used in the diagnosis and staging of many types of solid tumors, thus contributing to clinical decision making. The ability to noninvasively characterize in vivo molecular processes with a relatively fast whole-body scan is the major advantage of this technology. Picomolar concentration of RPhs offers accurate quantification of physiological, biochemical and pharmacological processes without disturbing them. Various radiotracers are used in different clinical situations. We sought to critically review the usefulness of PET-CT in patients with solid renal masses according to the aforementioned clinical challenges. We discuss the potential of radioimmunotherapy using RPhs for delivering high-energy isotopes to metastases.

MATERIALS AND METHODS

A PubMed search was conducted for articles published from 2004 through September 2015 using the keywords "renal," "kidney," "mass," "tumor," "cancer," and "PET/CT" with narrowing to English language publications in peer-reviewed scientific journals. Articles were selected according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) principles.[5] Reports were included if they contributed data regarding the previously mentioned clinical questions. Prospective studies were preferred whenever available. Retrospective studies and case reports were cited to fill gaps in knowledge when no prospective studies were available.

RESULTS

A total of 158 studies evaluating the role of PET-CT in patients with kidney cancer were identified. Only a few studies were designed to answer a specific clinical question. Additionally several articles were retrospective, and, therefore, biased due to preselection for lesions suspected or known for malignancy. All articles were analyzed and divided into groups according to clinical question, ie primary diagnosis of solid renal masses, identification of clear cell RCC, systemic evaluation for metastases, predicting prognosis and response to targeted therapy, posttreatment evaluation and future perspectives. An additional subdivision was performed according to the RPh used for PET-CT. We briefly describe RPhs commonly used for imaging of kidney cancer and address the associated clinical challenges.

Radiopharmaceuticals

The type and quality of the images produced by PET-CT are products of a complex interplay