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Molecular Imaging of Renal Cell Carcinoma: A Comprehensive Review

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Abstract

Renal Cell Carcinoma (RCC) represents a significant cause of cancer related deaths in the United States and worldwide. Current conventional imaging modalities including Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) reveal high resolution images of structural abnormalities; but these same modalities often fail to provide the adequate accuracy, specificity and sensitivity for diagnosing RCC from benign lesions. This has prompted ongoing investigation of molecular imaging modalities as a non-invasive alternative to biopsy. Initial use of glucose-based imaging agents has proven insufficient for common RCC histologies which have led to the development of targeted radiotracers to improve sensitivity of these scans. Current trials are ongoing to characterize the best use of these new targeted agents. In addition, novel radiotracer agents to evaluate renal perfusion, renal tubular function are being created and investigated.

Introduction

Renal cell carcinoma

In 2013 there were estimated to be 65,150 new cases of and 13,680 deaths due to cancer of the kidney and renal pelvis in the United States, representing about 4% of all cancers in adults [1]. Despite this, the worldwide incidence and mortality of kidney cancer has shown signs of stabilization when compared to the past two decades [2]. RCC originates from the renal tubules and can give rise to different histology types including oncocytoma, angiomyolipoma, papillary, chromophobe and clear cell renal carcinoma (ccRCC). Different morphologic and phenotypic characteristics as well as the associated metabolic and genetic derangements involved in each tumor help stratify these histologic RCC subtypes [3,4] of renal tumors of all sizes about 13% are benign (oncocytoma and angiomyolipoma) and about 87% are malignant (papillary, chromophobe and clear cell), with papillary type 1 and chromophobe carcinoma being relatively indolent with more limited metastatic potential whereas papillary type 2 and clear cell carcinoma typically are more aggressive with greater metastatic potential [4-6]. Among these malignant tumors, clear cell represents the most common histologic subtype followed by papillary and chromophobe [7].

The increased use of advanced cross-sectional imaging modalities has led to the incidental discovery of more renal tumors [8,9]. With the advent and wide proliferation of improved anatomical imaging such as CT scanning and MRI, the greatest increase in diagnosis of renal masses has been among tumors less than 4 cm in size [10]. Conventional imaging modalities currently in use for evaluation of patients with known renal lesions cannot accurately distinguish RCC from a solid benign lesion such as oncocytoma, creating a diagnostic and management dilemma for physicians. Furthermore, current imaging modalities cannot give information on metastatic potential or even intra-tumoral cellular proliferation. CT and MRI both have high sensitivity but limited specificity for diagnosing RCC and identifying lesions best managed with surgery as opposed to surveillance [11,12]. Ultrasound or CT guided biopsies represent alternative methods of sampling tumor specimens in order to accurately diagnosis RCC, however these methods are invasive, have a small but clinically relevant incidence of complications, and are non-diagnostic in 10-20% of cases (inversely correlated to tumor size) [13-16]. Furthermore it has been shown with small renal masses (SRMs) that up to 25% will be benign if biopsied [14,16]. In addition, the rate of metastasis for SRMs has been shown to be very low thus Active Surveillance (AS) has become increasingly more accepted as a therapeutic option in addition to surgery or ablation [17,18]. However, finding the balance between the risk of intervention and the risk of potential metastases has been the difficult challenge in the management of SRMs.

In light of the limitations of current imaging and biopsies, better non-invasive methods of diagnosing the RCC variants with the greatest malignant potential are needed. Molecular imaging of RCC holds promise in potentially yielding more information than currently available conventional imaging modalities, and the current targets and results of molecular imaging research in RCC will be reviewed.

Positron Emission Tomography

FDG-PET in renal cell carcinoma

Positron Emission Tomography (PET) is a nuclear medicine technique based on the detection and quantification of radiation levels emitted from radiotracers attached to metabolic substrates or receptor ligands. These agents are used to provide information regarding a tumor's biological features such as cell proliferation, metabolism and hypoxia [19,20] [18F]–fluorodeoxyglucose (FDG) is the most commonly used PET radiotracer for oncologic PET imaging [21]. Similar to glucose, FDG is transported into the cell and phosphorylated by a hexokinase. However, it is not metabolized any further and accumulates within the cell. Because tumors are typically more dependent upon glucose metabolism for energy as described by Warburg et al [22], as well as the fact that tumor cells generally have higher metabolic rates as a consequence of uncontrolled proliferation,

FDG-PET often shows greater uptake by tumor cells. An initial series by Bachor et al. described that FDG-PET had a sensitivity of 77% for detecting primary renal carcinomas [23]. Many other publications have evaluated the role of FDG-PET in the characterization of renal lesions, but most of these studies have failed to evaluate a population of patients that are of a "truly indeterminate" nature and thus are really pre-surgical candidates based on their CT scans. Therefore, data from these publications does not really answer the question of how to better characterize indeterminate renal lesions. A more recent study by Ozulker et al, prospectively evaluated 18 patients to determine the efficacy of FDG-PET in the detection of in patients with indeterminate who subsequently underwent surgical resection of their renal masses. In their series, PET showed a sensitivity of 46.6%, specificity of 66.6%, and accuracy of 50% for detection of these primary renal cell tumors, majority (94%) of which were of clear cell histology [24]. This most recent publication suggests a questionable role of FDG-PET for imaging indeterminate renal masses, but larger studies are required to validate their results.

In addition to its possible role as a diagnostic tool in primary RCC, FDG-PET has been described as a useful tool for the detection of local recurrence and metastasis [25,26] Safaei et al reported a sensitivity and specificity of 82% and 88% respectively for FDG-PET for the staging of 36 patients with advanced RCC (based on biopsy proven lesions) [27]. Additionally, Majhail and coworkers reported that for detection of distant metastasis, FDG-PET only had a sensitivity of 63.6% but a specificity of 100% [28]. In a larger series of 66 patients, Kang et al described that FDG-PET was outperformed by CT in terms of sensitivity for detection of retroperitoneal lymph nodes and renal bed recurrences (75% for FDG-PET vs 92.6% for CT), lung metastasis (75% vs 91.1%) and bony metastasis (77.3% vs 93.8%) [29]. In a more recent series, Nakatani et al evaluated the performance of FDG-PET for detection of recurrence, with better results. Twenty-three patients underwent FDG-PET scans at least 6 months after surgery. They found 16 patients with demonstrated recurrence for RCC. The overall sensitivity, specificity and accuracy of FDG-PET for detection of recurrence were 81%, 71% and 79% respectively. They described that FDG-PET correctly detected local recurrence in peritoneum, bone, muscle and the adrenal gland [30]. There were several limitations to this study, including its retrospective nature and small number of patients. However, it suggests a possible role for FDG-PET in the setting of detection of recurrence of RCC. In 2012, Wang et al published a meta-analysis describing the diagnostic performance of FDG-PET and PET/CT in RCC. They included 14 studies in their analysis and reported a pooled sensitivity and specificity for FDG-PET in RCC of 62% and 88% [31]. When looking at detection of extra-renal lesions, the pooled sensitivity and specificity was 79% and 90% respectively when based on the scans. Furthermore, they report that the sensitivity and specificity was improved when a hybrid FDG-PET/CT was used to detect extra-renal lesions, reaching 91% and 88% respectively. Based on these results, the authors suggest that FDG-PET in combination with CT is helpful in detecting extra renal metastasis from RCC but further evidence is needed to investigate use for primary renal lesions.

While the role of FDG-PET in localized and metastatic clear cell RCC may still be unclear, there are other histologies for which FDG-PET may have better performance characteristics and therefore greater application. Several variants of RCC have been found to result from mutations in the Krebs cycle enzymes. For example, germline alterations of the enzyme fumarate hydratase within the Krebs cycle has been associated with papillary type II renal cell carcinoma in patients with hereditary leiomyomatosis and renal cell cancer (HLRCC) [32-34]. Due to the Warburg effect, these tumors are entirely dependent on aerobic glycolysis resulting in exceptionally high glucose utilization [22]. In addition, hereditary succinate dehydrogenase-related renal tumors also appear to be reliant on aerobic glycolysis due to disruption of the Krebs cycle [35]. This dependence on glucose for proliferation theoretically makes these types of tumors particularly good FDG-PET targets; and recently data supporting this hypothesis has been presented [36]. Larger prospective studies are required to better characterize this data. Nonetheless, these findings demonstrate that understanding the genetic and metabolic derangements within tumors can guide not only therapy but also decisions regarding which diagnostic modalities are most appropriate.

In addition to FDG, other PET tracers have also been investigated. Oyama et al showed that 11C-acetate, a tracer already found to have high uptake in prostate cancer before treatment, had increased uptake in a size- dependent manner in a small cohort of 20 patients with renal tumors[37,38] 18F-fluorothymidine, a radioisotope based on the nucleic acid thymidine which has been found to be a promising tracer in other human cancers, was shown to accurately identify RCC in a single patient case report [39] Finally 18F-fluoromisonidazole, a compound whose tissue retention and metabolism relies on the amount of tissue oxygenation, was found to have only mild tumor uptake in a cohort of 11 patients with RCC [40]. Although these PET tracers have demonstrated some accuracy in detecting RCC, their specific roles have not been studied in larger patient trials.

Carbonic anhydrase IX

Carbonic anhydrase ix expression and renal cell carcinoma

Clear cell Renal Cell Carcinoma (ccRCC) represents the most prevalent histologic subtype of renal cell adenocarcinoma. The metabolic pathway underlying ccRCC has been extensively studied. Germline mutations in the von Hippel-Lindau (VHL) gene in patients with VHL disease gives rise to the hereditary form of clear cell renal carcinoma, and similarly methylation or mutation of the VHL gene is present in about 90 percent of tumors in patients with sporadic clear cell kidney cancer[3,41-43]. Carbonic anhydrase IX (CAIX), a transmembrane and cytosolic glycoprotein involved in the regulation of pH and acid-base balance within the body, expression is molecularly linked to the Von Hippel-Lindau protein (pVHL) and has been shown to be regulated by the transcription factor hypoxia-inducible factor-1α (HIF-1α) [44]. In a normal oxygenated environment HIF-1α is hydroxylated by propyl hydroxylase domain proteins and then bound by pVHL, leading to the ubiquination and subsequent degradation of HIF-1α. However, in a hypoxic environment the binding of HIF-1α to pVHL is inhibited, allowing the formation of the HIF-1α- HIF-1β dimer complex, accumulation of HIF-1 and the ensuing transcription of several hypoxia-inducible genes including CAIX [45]. These metabolic and genetic derangements as well as the presence of hypoxia both result in the downstream effects and subsequent cell transformation in ccRCC. The reduction in tumor hypoxia after sunitinib therapy, evaluated using 18F-fluoromisonidazole PET/CT, described in a cohort of metastatic RCC (mRCC) patients further highlights the inextricably link between hypoxia and the metabolic basis of kidney cancer[46].

Immunochemistry and reverse transcription-polymerase chain reaction have been used to determine the level of CAIX antigen expression in the different RCC histologic subtypes. CAIX was found

to be a potential marker for ccRCC, demonstrating high and homogenous levels of expression in majority of the tumors, whereas its expression in oncocytomas, papillary and chromophobe RCC was significantly lower [47,48]. CAIX expression is also present in some normal tissues including gastric mucosa, pancreatobiliary epithelium, small intestine crypt base, mesothelial cells, ovarian surface epithelium and fetal rete testis, but not in normal kidney tissue [45,48]. The molecular association between CAIX and pVHL and the nearly uniform mutational loss of the VHL gene seen in ccRCC with the resultant downstream effects explains the ubiquitous expression of the CAIX antigen in ccRCC [49].

Carbonic anhydrase ix expression and prognostic value

Several studies have reported correlations with low CAIX expression and poor outcomes in patients with RCC, with overexpression of CAIX yielding a more favorable prognosis in these patients [50-54] Bui et al showed that in metastatic ccRCC patients, after adjusting for primary tumor classification, Fuhrman grade, nodal status and Eastern Cooperative Oncology Group (ECOG) performance status, that low CAIX expression was associated with an increased risk of death [50]. This same group also reported, after multivariate analysis, that low CAIX expression in conjunction with high Ki-67 (a nuclear protein associated with cell proliferation) was significantly correlated with a poor median RCC-specific survival [51].

However, Leibovich et al found that in 730 surgically treated patients with unilateral sporadic ccRCC, after adjusting for pathologic features including nuclear grade or coagulative tumor necrosis, that CAIX was not an independent predictor of outcome in patients with ccRCC [48]. This same group recently did an additional 5-year follow up on the same patient cohort confirming their initial result that CAIX is not an independent prognostic marker for ccRCC [55]. In addition, the prospective data from the SELECT trial has not reported any useful biomarkers for predicting response to immunotherapy [56]. Given these contradicting studies, additional studies are needed to elucidate the actual prognostic value of CAIX.

Carbonic anhydrase ix diagnostic imaging

In 1986, an immunohistochemical study done by Oosterwijik et al first described the recognition of a tumor antigen, present on RCC cells and not on normal renal cells, by a monoclonal antibody G250 (MAb G250) [57]. This finding suggested the potential for this MAb G250 recognized moiety for future radioimmunodetection. The G250-antigen was later found to be an isoenzyme of the carbonic anhydrase family and identical to MN/CAIX, a tumor associated antigen of the cervix [58].

Numerous clinical trials have been conducted with different radiotracers to determine the diagnostic accuracy of MAb G250 in ccRCC. Steffens et al determined the pharmokinetics, toxicity, immunogenicitiy and imaging characteristics of 131I-labeled chimeric MAb G250 (girentuximab) in primary ccRCC patients prior to nephrectomy. This study showed that at the optimum protein dose of 5-10mg, excellent visualization of primary and metastatic G250-antigen positive tumors was attained in all 13 patients [59]. When RadioImmunoScintigraphy (RIS) with 131I-labeled chimeric MAb G250 was then compared with [18F] FDG-PET for detecting known metastatic lesions in RCC patients, it was found that the 131I-labeled chimeric MAb G250 identified only 30%, whereas [18F] FDG-PET detected almost 70% of these lesions [60]. A comparative intrapatient study in mRCC patients further showed that radiometal 111In-labeled cG250 detected 47 metastatic lesions compared to 131I-labeled cG250 which detected 30 metastatic lesions. The better imaging detection and increased tumor:blood ratios noted in this study were attributed to the difference in internalization and metabolism of the radiolabeled MAb, with the catabolite of 131I-cG250 being rapidly excreted from the tumor cells and the catabolite of 111I-ITC-DTPA-cG250 being retained in the tumor cells [61]. In a retrospective analysis of 22 patients, 111In-girentuximab immune-single positron emission computed tomography (immunoSPECT) was also shown to be a useful non-invasive tool for detecting indeterminate primary ccRCC lesions and for characterizing lesions suspicious for metastasis [62].

Immuno-PET, which combines MAb cG250 identification with the good features of PET imaging, has been studied with the positron emitter 124I. In a Phase I prospective clinical trial in 26 patients prior to nephrectomy, Divgi et al showed that 124I-cG250 immuno-PET detected 15 out of the 16 ccRCC lesions resulting in a sensitivity of 94% (95% CI 70–100%), specificity of 100% (95% CI 66–100%), positive predictive value of 100% (95% CI 78–100%) and negative predictive value of 90% (95% CI 55–100) [63]. They concluded that 124I-cG250 immuno-PET can be an effective method for characterizing renal lesions thereby helping guide clinical decision making and surgical management. Another study examined the surgical specimens from this Phase I clinical trial and found that in vivo quantification of CAIX antigen expression and 124I-cG250 binding with PET/CT correlated strongly with in vitro measurements of these parameters, highlighting further the potential for immunoPET in antibody based therapies [64]. A more recent large multicenter prospective Phase III clinical trial (REDECT trial) showed that 124I-cG250 PET/CT was superior to contrast-enhanced CT (CECT) in identifying ccRCC in patients prior to nephrectomy. For 124I-cG250 PET/CT and CECT readers in all 14 centers in the REDECT trial, the average sensitivity was 86.2% and 75.5% (P=.023) respectively and the average specificity was 85.9% and 46.8% (P=.005) respectively [4,65].

Other studies have outlined the advances in the use CAIX for targeted radio-immunotherapy for ccRCC [66], however this topic is beyond the scope of this manuscript.

Conclusion

RCC continues to be an important cause of cancer-specific mortality in the United States, necessitating the need for better diagnostic accuracy, clinical decision making and treatment for RCC patients. Molecular imaging modalities represent a non-invasive alternative option for improving the specificity and sensitivity of diagnosing RCC when compared to conventional imaging modalities (CT and MRI) and invasive diagnostic biopsies.

FDG-PET has extensive use in oncologic imaging due to the increased glucose metabolism seen in most tumors. One disadvantage of FDG-PET use in renal imaging is that FDG is excreted by the kidneys and therefore causes an increased amount of background activity, which is minimally helped by diuretic administration and excessive hydration. FDG-PET has not been shown to be great modality for identifying primary renal lesions, but a recent meta-analysis showed that FDG-PET/CT is superior in detecting extra-renal metastasis from RCC. This study clearly delineated the role of FDG-PET in identifying extra-renal tumors, however larger clinical trials for RCC patients with truly indeterminate renal tumors are needed to

confirm its role in primary RCC. Very limited studies have been done with other PET tracers and diagnostic imaging for RCC.

Clear cell RCC represents an aggressive histologic sub-type of RCC. The high expression of the transmembrane and cytosolic glycoprotein CAIX in ccRCC has been pivotal for the advances in radioimmunodetection with the chimeric MAb G250. The use of the positron emitter 124I in combination with PET imaging has demonstrated great diagnostic utility, with the recent multicenter REDECT trial showing the accuracy of 124I-cG250 PET/CT in identifying ccRCC with an average estimated sensitivity and specificity of 86.2% and 85.9% respectively. Future directions includes a head to head comparison of 124I-cG250, 111In-cG250 and FDG-PET in detecting ccRCC, as no studies have been done directly comparing these agents. Additionally a study looking at the size detection limits of 124I-cG250 PET/CT and its use in patients who are not considered to be pre-surgical will be imperative for further investigation of this imaging method.

Molecular imaging modalities have been continually investigated for use in diagnosing RCC. Further work in this area is important for determining the role of these modalities in improving the diagnostic accuracy and subsequent clinical management of patients with RCC.

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