applied sciences

MDPI

Review

Current Imaging Evaluation of Tumor Response to Advanced Medical Treatment in Metastatic Renal-Cell Carcinoma: Clinical Implications

Martina Caruso [1,*], Valeria Romeo [1], Arnaldo Stanzione [1], Carlo Buonerba [2], Giuseppe Di Lorenzo [3,4] and Simone Maurea [1]

[1] Department of Advanced Biomedical Sciences, University of Naples "Federico II", Via S. Pansini, 5, 80131 Naples, Italy; valeria.romeo@unina.it (V.R.); arnaldo.stanzione@unina.it (A.S.); maurea@unina.it (S.M.)
[2] Regional Reference Center for Rare Tumors, Department of Oncology and Hematology, AOU "Federico II" of Naples, Via S. Pansini, 5, 80131 Naples, Italy; carbuone@hotmail.com
[3] Oncology Unit, Andrea Tortora Hospital, ASL Salerno, 84016 Pagani, Italy; dilorengiuseppe@gmail.com
[4] Vincenzo Tiberio, Department of Medicine & Health Sciences, University of Molise, 86100 Campobasso, Italy
* Correspondence: caruso.martina90@gmail.com; Tel.: +39-0817463560

Abstract: The present review is focused on the role of diagnostic tomographic imaging such as computed tomography and magnetic resonance imaging to assess and predict tumor response to advanced medical treatments in metastatic renal cell carcinoma (RCC) patients. In this regard, antiangiogenic agents and immune checkpoint inhibitors (ICIs) have developed as advanced treatment options replacing the conventional therapy based on interferon-alpha and interleuchin-2 which had unfavorable toxicity profile and low response rates. In clinical practice, the imaging evaluation of treatment response in cancer patients is based on dimensional changes of tumor lesions in sequential scans; in particular, Response Evaluation Criteria in Solid Tumors (RECIST) have been defined for this purpose and also applied in patients with metastatic RCC. However, these new drugs with predominant cytostatic effect make RECIST insufficient to realize an adequate response imaging evaluation. Therefore, new imaging criteria (mCHOI and iRECIST) have been proposed to assess tumor response to advanced medical treatments of metastatic RCC, they correlate better than RECIST with the progression-free survival and overall survival. Finally, a potential role of radiomics and machine learning models has been suggested to predict tumor response.

Keywords: kidney cancer; computed tomography; magnetic resonance imaging; radiomics; prediction tumor response

Citation: Caruso, M.; Romeo, V.; Stanzione, A.; Buonerba, C.; Di Lorenzo, G.; Maurea, S. Current Imaging Evaluation of Tumor Response to Advanced Medical Treatment in Metastatic Renal-Cell Carcinoma: Clinical Implications. *Appl. Sci.* **2021**, *11*, 6930. https://doi.org/10.3390/app11156930

Academic Editor: Francesco Bianconi

Received: 29 May 2021
Accepted: 26 July 2021
Published: 28 July 2021

1. Introduction

Renal cell carcinoma (RCC) accounts for 2% of global cancer diagnoses per year with an estimated 403,000 cases; in particular, its prevalence is progressively increasing with an average of 1.4% per year [1]. In this scenario, the imaging evaluation of patients with such neoplastic disease plays a crucial role for tumor diagnosis and staging as well as for the evaluation of therapy response. While representing a common incidental finding in abdominal ultrasound, RCC requires cross-sectional imaging exams, such as computed tomography (CT) and/or magnetic resonance imaging (MRI), for better tumor characterization and accurate disease staging. At diagnosis, CT and MRI can characterize morphologic RCC features such as tumor size, precise location, feeding vessels, presence of a pseudocapsule, local extension in (e.g., vessels, Gerota's fascia and/or peri-renal fat involvement) and nodal status. Contrast-enhanced CT is usually preferred due to wide availability, high resolution and acquisition speed, as well as for the detection of distant metastasis. On the other hand, MRI can aid in the characterization of RCC due to its multi-parametricity and multi-planarity [2].

For resectable RCCs at imaging baseline, surgery represents the standard of care, while systemic medical therapies may be used in patients with surgically unresectable or metastatic RCC [3]. In patients surgically treated, the follow-up imaging assessment is finalized to early detect loco-regional relapse or distant metastasis, while in those medically treated to assess therapy response and disease course. Unfortunately, a substantial percentage of RCC patients show metastatic disease. In particular, an estimated 18% have metastatic lesions at diagnosis, while more than 50% develop them after nephrectomy usually within 3 years from initial diagnosis [4]. Unfortunately, these latter patients have a 2-year survival rate of 10–20% [5]. However, new drugs such as antiangiogenic therapies and immune checkpoint inhibitors (ICIs) have contributed to redefine the medical management of metastatic RCC in the last decades.

The aim of the present review is to illustrate the diagnostic role of tomographic imaging in the assessment and prediction of tumor response to advanced medical treatments in metastatic RCC patients.

2. Advanced Medical Treatments in Metastatic RCC: Mechanisms of Action

According to the pathogenetic mechanisms and molecular basis of RCC, antiangiogenic agents and ICIs have developed as advanced treatment options [3]. These drugs have replaced the conventional therapy based on interferon-alpha and interleuchin-2 which had unfavorable toxicity profile and low response rates (10–20%) [6]. These new agents have mainly a cytostatic effect inducing tumor stabilization and/or slow regression, unlike cytotoxic compounds, that may induce complete tumor regression.

Most commonly used antiangiogenic agents for the treatment of metastatic RCC are represented by sunitinib, pazopanib, cabozantinib, lenvatinib and axitinib [7]. These tyrosine kinase inhibitors target the vascular endothelial growth factor pathways involved in tumor neoangiogenesis, the process by which RCC generates its own irregular and immature microvascular network [5]. In particular, the upregulation of the vascular endothelial growth factor and the inactivation of the Von Hippel Lindau contribute to neoangiogenesis in RCC. Antiangiogenic agents decrease tumor perfusion blocking the aforementioned pathway, even though having limited efficacy in reducing the tumor lesion in size for the main cytostatic effect [8]. For these reasons, complete response occurs rarely (<1%), while minor response and disease stabilization are very frequent (>70% of cases) [5]. Furthermore, clear cell RCC, the most common (75%) RCC histological subtype, is associated with somatic/hereditary mutations or deletions in the Von Hippel Lindau gene region and are expected to respond better [9]. On the other hand, papillary RCC may also get benefits from antiangiogenic agents if the gene encoding fumarate hydratase is mutant [10].

The most promising ICIs approved for metastatic RCC include anti PD-1 agents, such as pembrolizumab, to be administered with axitinib, and nivolumab (anti-PD-1), to be administered alone or with ipilimumab (an anti-CTLA-4 agent) or with cabozantinib, and anti-PDL-1 agents such as avelumab, to be administered in combination with axitinib [11,12]. ICIs consist of innovative cancer immunotherapy agents, downregulating multiple immune checkpoints, such as CTLA-4 and PD-1, expressed by different immune cells, in this way they rehabilitate exhausted T cells which recover toxicity against tumor cells. These agents also regulate the T cell trafficking and migration [13]. ICIs provide a long-term immune protection because they induce a memory cell response, so, unlike chemotherapy, their effects continue even after stopping the treatment [14]. The specific and targeted mechanism of action allows an improvement in the overall survival with fewer side effects compared with initially approved drugs, like everolimus, in patients with advanced RCC; however, the reported objective response rate to ICIs is 25% [15].

3. Imaging Evaluation of Therapy Response in Metastatic RCC

In oncology, imaging is widely employed to assess treatment response and guide patient management [16]. CT represents an accurate imaging modality for this purpose,

often preferred to MRI because its total-body acquisition allows to detect potential distant metastases. Usually, the imaging assessment of treatment response or disease progression in cancer patients is performed by dimensional evaluation of tumor burden in consecutive scans; in particular, Response Evaluation Criteria in Solid Tumors (RECIST) have been embraced for this purpose and also applied in patients with metastatic RCC [17]. Of note, these criteria have been proposed to standardize and objectively assess solid tumor measurements both in adult and pediatric cancer clinical trials where tumor response is required. As a consequence, in daily clinical practice many oncologists have adopted these criteria to evaluate imaging studies during the follow-up, but physicians make decisions about treatment strategies also considering clinical criteria. In detail, RECIST identifies measurable and non-measurable tumor lesions with the former including lesions having a longest diameter of $\geq$10 mm and the latter including small lesions ($\leq$10 mm), skeletal metastases, leptomeningeal disease, ascites, pleural and pericardial effusions. Hence, for the assessment of treatment response target and non-target lesions are usually identified with the former represented by measurable lesions, up to a maximum of five total lesions as well as a maximum of two lesions per organ, and the latter including all tumor lesions not chosen as target lesions. On the basis of dimensional lesion changes during the follow-up, the disease is classified as stable, in progression, with partial or complete response. Nowadays, the introduction of innovative drugs with predominant cytostatic effect makes RECIST, dimensional criteria, insufficient to get an adequate response imaging evaluation. First of all, they do not include early indicators of tumor response; of note, the anatomic assessment may take more time to detect any shrinkage unlike use of functional hybrid imaging exams, that may show tumor changes earlier. Secondly, RECIST do not have a clinical validation to be used in the response assessment to novel agents; surprisingly, a low response rate has been reported for many patients with metastatic RCC, despite a higher numbers of cases with prolonged stable disease and improved survival compared to conventional treatment protocols [10]. Hence, RECIST might underestimate the tumor response to these innovative drugs as well as the RECIST system does not include recent advanced imaging techniques, frequently considered in clinical trials, able to assess tumor micro-environment and atypical tumor response patterns which may occur using antiangiogenic agents and/or ICIs [18]. Therefore, considering these aforementioned limitations of RECIST, the widespread of advanced targeted therapies and the need to answer to specific clinical issues, new imaging criteria are needed.

Moreover, going beyond the visual image evaluation, the emergence of radiomics has shown the potential to further increase the value of CT and MRI for treatment response assessment [19]. Radiomics is a complex multi-step process that aims to extract a large number of quantitative features from digital medical images, allowing to quantitatively explore tumor heterogeneity which reflects its underlying pathophysiology. Radiomic features integrated or not with clinical data can be used to build machine learning models which can potentially aid the physicians in clinical practice by improving diagnostic, prognostic, and predictive accuracy [19]. In particular, texture analysis features assess the spatial distribution of pixel intensity levels within an image, the obtained quantitative data reflect the image heterogeneity. To date, a role of radiomics and machine learning has been suggested in the prediction of Fuhrman grade in clear cell RCC and/or in the prediction of tumor response in metastatic RCC patients treated with nivolumab [20,21].

3.1. Antiangiogenic Therapies

As previously described, antiangiogenic drugs achieve a cytostatic effect reducing tumor perfusion and consequently inducing lesion necrosis. In this setting, different studies highlighted that changes in tumor CT attenuation values anticipate changes in lesion size, predicting treatment response. In particular, Han et al. noticed that higher response rates correlates with higher CT enhancement values of metastases before treatment, as well as Baccala et al. found that the presence of necrosis, as CT hypodensity, was associated with more favorable therapeutic outcome [22,23]. Conversely, the appearance of central

areas of enhancement in previously hypodense lesions during treatment was indicative of disease progression [24]. For these reasons and for the cytostatic effect of antiangiogenic therapies, RECIST, based only on dimensional evaluation of tumor burden, are not accurate to assess such treatment response. New imaging criteria, firstly Choi and then modified Choi (mCHOI), have been proposed for this purpose (Table 1) [17,25,26]. In particular, Thian et al. compared the assessment of tumor response in metastatic RCC patients treated with sunitinib according to RECIST, CHOI and mCHOI criteria. All of these three different criteria assess treatment response by measuring tumor burden as the sum of the target lesions diameters, but the most important difference among these three criteria is the evaluation of partial response (PR) for which RECIST consider only significant changes in tumor size (≥30%), while CHOI and mCHOI account for slight changes in tumor size (≥10%) alternatively present with tumor CT density decrease (≥15%) (CHOI) or associated with tumor CT density decrease (≥15%) (mCHOI). Thus, not only tumor size changes, but also tumor density changes are considered in these new treatment response criteria. In this regard, Thian et al. reported in their systematic study that only mCHOI criteria were able to accurately stratify patients for both overall survival and progression-free survival (PFS) better correlating with the clinical outcome compared to CHOI and RECIST criteria [26]. Therefore, these new criteria (CHOI and mCHOI) account for tumor response morpho-structural tumor changes represented by changes in lesion size and/or CT density; this novel approach seems to be more accurate than RECIST since CT density tumor changes may be earlier than changes in lesion size; thus, CHOI and mCHOI may be able to early identify responders patients to antiangiogenic therapies, even though significant decrease of tumor burden is not observed. However, some methodological CT aspects should be underlined since these may influence imaging results, potentially limiting the accuracy of these criteria; in this regard, scanning time, concentration of contrast medium and measurement of CT density have yet not been standardized for these purposes.

Table 1. Imaging tumor response criteria to antiangiogenic therapies.

Response	RECIST 1.1 [17]	Choi Criteria [25]	Modified Choi Criteria [26]
Complete Response (CR)	No evidence of target and non-target lesions; Short axis of lymph node(s) < 10 mm; No new lesions.	No evidence of target and non-target lesions; Short axis of lymph node(s) < 10 mm; No new lesions.	No evidence of target and non-target lesions; Short axis of lymph node(s) < 10 mm; No new lesions.
Partial Response (PR)	Decreased (≥30%) sum of target lesions longest diameters.	Decreased (≥10%) sum of the target lesions longest diameters OR Decreased (≥15%) tumor density (HU).	Decreased (≥10%) sum of the target lesions longest diameters AND Decreased (≥15%) tumor density (HU). Decreased (≥30%) sum of the target lesions longest diameters.
Stable Disease (SD)	Not PR/PD.	Not PR/PD.	Not PR/PD.
Progressive Disease (PD)	Increased (≥20%) sum of the target lesions longest diameters; Evidence of new lesion(s).	Increased (≥10%) sum of the target lesions longest diameters and not PR by tumor density; Evidence of new lesion(s). New intratumoral nodules or increase in size of the previous intratumoral nodules.	Increased (≥10%) sum of the longest diameters of target lesions; New lesions or intratumoral nodules.

The specific action mechanism of antiangiogenic agents explains the atypical response patterns and radiologists have to know them to avoid pitfalls. Sometimes the increase in

size of metastatic lesions is due to intratumoral edema or necrosis induced by therapy and not to disease progression, as expected; other times, lesions increase in size and attenuation due to intratumoral hemorrhage induced by starvation of blood supply. In particular, the appearance of a fluid–fluid level within the lesion is expression of intratumoral hemorrhage, MRI may be helpful to identify blood in such cases [10]. The appearance of new lesions is the most misleading atypical response pattern; sometimes metastatic lesions may not be identified at baseline because they have the same density of the surrounding parenchyma, but after treatment they may be detectable as a result of decreased (edema or necrosis) or increased (hemorrhage) CT attenuation [10]. Moreover, the sharp and smooth margins of the lesions represent a useful sign of good response during follow-up [10]. To date, even though the atypical response patterns incidence is not well known, radiologists should take them into account when evaluating patients in treatment with antiangiogenic drugs. The evaluation of all lesions' behaviors and the correlation with clinical data are often useful; in case of doubt, a CT revaluation after a few weeks (6–8) can be suggested [10].

Since antiangiogenic therapy affects tumor perfusion, the non-invasive assessment of tumor vascularity represents a challenging endpoint for radiologists that could provide information of treatment response. Perfusion parameters can be assessed by using contrast-enhanced ultrasound and dynamic contrast-enhanced CT, as well as non-enhanced MRI (arterial spin-labeling MR imaging) and dynamic contrast-enhanced MRI sequences. The dynamic contrast-enhanced imaging techniques are based on the temporal changes in tumor tissue echogenicity/attenuation/intensity after intravenous administration of contrast medium as a bolus. The parameters of microcirculation (tissue blood flow and volume, tissue interstitial volume and mean transit time) are extracted from the tumor tissue enhancement curves. Among the imaging techniques, the CT perfusion approach is preferred for different reasons. First, it is easy to implement because there is a direct correlation between attenuation (HU) and concentration of contrast agent, obtaining perfusion parameters by mathematical models [8]. Secondly, since multidetector CT equipment have a large anatomic coverage and RCC metastases usually appear in the lung bases and in the upper abdomen, all lesions can be assessed in the same acquisition, unlike MRI and ultrasound which usually allow to evaluate one anatomic district [5]. Perfusion changes as well as attenuation modifications normally precede changes in size, so perfusion CT could aid to assess therapy response and to identify non-responder patients at an earlier point. Furthermore, the means of blood flow measurements allow to identify focal areas of new tumor perfusion, expression of resistance and/or of progressive disease. Based on perfusion parameters, clinicians could modify dose and schedule of the therapy or switch to another drug [27]. Even though perfusion CT parameters turned out to be a non-invasive early indicator of efficacy of antiangiogenic therapy, they currently remain investigational and their role in clinical practice has not been yet defined [28]. Figure 1 illustrates an example of a patient with metastatic clear cell RCC treated with antiangiogenic drugs showing SD (Table 1).

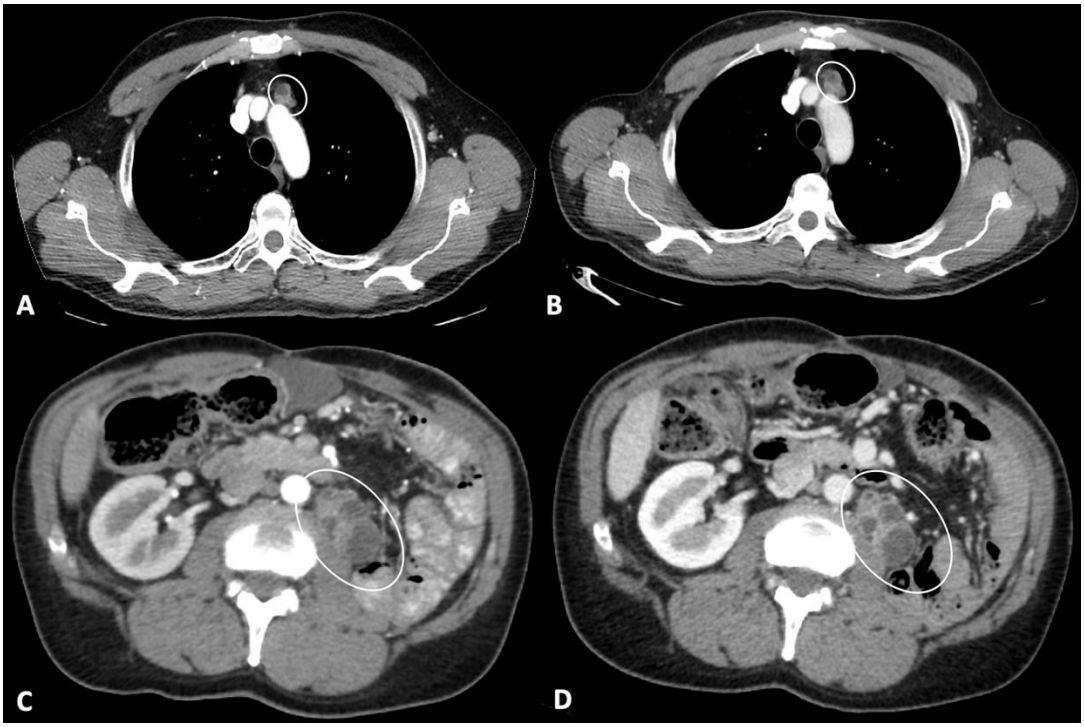

Figure 1. CT axial scans in a male patient, 59 years old, with chest and abdominal lymph node metastases before (**A**,**C**) and after (**B**,**D**) medical treatment. The patient underwent left nephrectomy for the primary tumor (clear cell RCC) and was medically treated with cabozantinib (60 mg/die) when disease recurrence occurred during the post-surgical follow-up. CT images show chest (**A**,**B**) and abdominal para-aortic (**C**,**D**) partially necrotic lymphoadenopathies which remained stable at re-evaluation as stable disease according to mCHOI criteria (Table 1).

3.2. Immune Checkpoint Inhibitors

As mentioned above, ICIs act through a novel immune-mediated mechanism with T-cell-activation. These drugs are cytostatic agents which induce a delayed and slow response compared with chemotherapy; thus, atypical response patterns can be observed. One of these is called pseudo-progression, which consists of a decrease in the total tumor burden after an initial increase or the appearance of new lesions [13]. In this regard, two possible explanations have been hypothesized, such as infiltration of T cells into tumor lesions or persisted tumor growth waiting an efficient immune response [29]. Of note, pseudo-progression may be misclassified as progressive tumor disease and should be taken into account in the response assessment of metastatic RCC patients in treatment with ICIs. However, it has to be highlighted that its incidence is low and more frequent in younger patients, and true progression is more likely than pseudo-progression when an increase of tumor burden is noticed [13]. Furthermore, it is to be underlined that the response duration is shorter in such patients than those with PR or CR, although they show better outcomes than patients with typical PD [30]. Another possible tumor response is the hyperprogression, consisting of extreme acceleration of tumor growth kinetics ($\geq$2-fold increase of tumor growth rate before and after therapy), more frequent with anti-PD1/PD-L1 agents [31]. The underlying mechanism of this type of response has not been elucidated yet, but a significant correlation with patients' age and decreased overall survival was found [32]. Finally, ICIs can induce a dissociated tumor response characterized by the increase in size of some lesions and the decrease in size of others; the pathophysiologic explanation of this phenomenon remains unknown, thus requiring a simultaneous evaluation of tumor burden and clinical data [29].

Although relatively uncommon, radiologists have to know these atypical response patterns of ICIs therapy so that treatment is not interrupted when new lesions appear or existing lesions increase in size until progressive disease is not confirmed on a second

follow-up scan. These atypical responses influence the clinical practice and new imaging response criteria should be considered, which include two fundamental concepts such as that a new lesion does not preclude PD and/or a confirmation of PD. In the last years different immune-adapted criteria have been suggested consisting of immune-related response criteria (irRC), immune-related RECIST (irRECIST) and immune-RECIST (iRECIST) (Table 2) [17,29,33,34]. In detail, irRC were the first immune-adapted criteria and the two major innovations were the following: new measurable lesions were included into the total tumor burden and the imaging revaluation after at least 4 weeks from the previous exam is necessary to define complete response (CR), partial response (PR) and progressive disease (PD). The irRECIST differed from irRC because the measurement of tumor burden was unidimensional and not bi-dimensional, improving reproducibility. The iRECIST introduced the novel concept of immune-unconfirmed PD (iUPD) which inspires the RECIST 1.1 PD and requires confirmation by imaging re-evaluation at 4–8 weeks, defining the immune-confirmed PD (iCPD) [34]. It could be assigned two times so long as iCPD criteria has not been met; during this time interval, therapy should continue, unless a clinical worsening occurs. Thus, iRECIST could capture atypical response, but it is important to underline that pseudo-progression is uncommon, so clinical decisions about the treatment strategy should be based mainly on patient medical status. Currently, in clinical trials iRECIST are the most encouraging criteria to assess response rate and PFS [35]. Figures 2 and 3 illustrate two examples of patients with metastatic clear cell RCC that have undergone ICIs treatment showing PR and iUPD, respectively (Table 2).

Table 2. Imaging tumor response criteria to ICIs.

Response	RECIST 1.1 [17]	irRC [29]	irRECIST [33]	iRECIST [34]
Dimension	One.	Two.	One.	One.
New measurable lesions	Designates PD.	New lesion(s) does not define PD; Incorporates into total tumor burden for the assessment of PD.	New lesion(s) does not define PD; Incorporates into total tumor burden for the assessment of PD.	Separately documents; adds into PD.
Complete Response (CR)	No evidence of target and non-target lesions; Short axis of lymph node(s) < 10 mm; No new lesions.	No evidence of target and non-target lesions in two consecutive exams (at least 4 weeks apart); Short axis of lymph node(s) < 10 mm; No new lesions.	No evidence of target and non-target lesions; Short axis of lymph node < 10 mm; Short axis of lymph node(s) < 10 mm; No new lesions.	No evidence of target and non-target lesions; Short axis of lymph node < 10 mm; Short axis of lymph node(s) < 10 mm; No new lesions.
Partial Response (PR) [a]	Decreased (≥30%) sum of target lesions longest diameters.	Decreased (≥50%) total tumor burden; Unclear non-target lesions progression.	Decrease (≥30%) in the sum of target lesions longest diameter; Unclear non-target lesions progression.	Decrease (≥30%) in the sum of target lesions longest diameter; Unclear non-target lesions progression.
Stable Disease (SD)	Not PR/PD.	Not PR/PD.	Not PR/PD.	Not PR/PD.
Progressive Disease (PD) [b]	Increased (≥20%) sum of the target lesions longest diameters; New lesion(s).	Increased (≥25%) total tumor burden.	Increased (≥20%) sum of the target lesions longest diameters; Increased non-target lesions.	iUPD: increased (≥20%; at least ≥5 mm) sum of the target lesions longest diameters; Increased non-target lesions.
Confirmation of PD (at least 4 weeks apart from the previous exam)	NA.	Increased (≥25%) in total tumor burden.	New clear progression or continued progression from the first PD; Evidence of new lesions.	iCPD: increased new target lesions (≥5 mm); Progression of target, non-target lesions and new non-target lesions; Evidence of new lesions. Presence of other new lesions.

[a] Referred to the baseline; [b] Referred to the nadir (minimum recorded tumor burden); iUPD: immune-unconfirmed progressive disease; iCPD: immune-confirmed progressive disease.

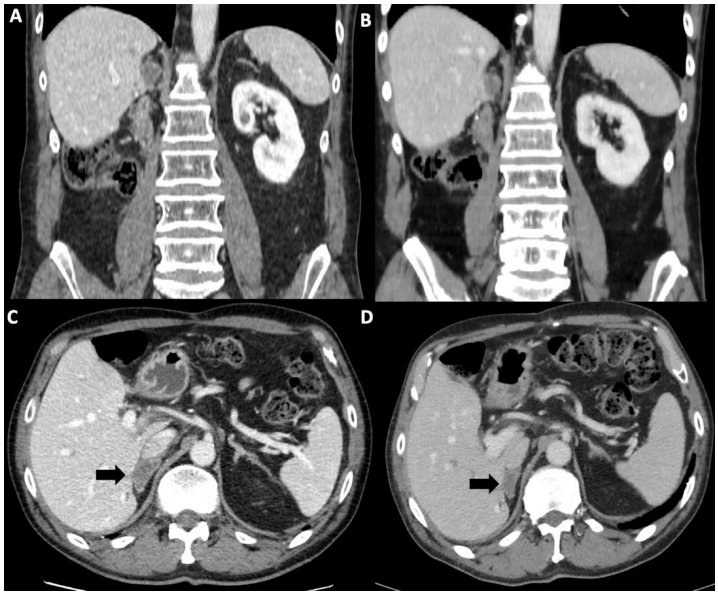

Figure 2. CT scans in a male patient, 69 years old, with metastatic RCC in the right adrenal gland before (**A**,**C**) and after medical treatment (**B**,**D**). CT images are reported in coronal views (**A**,**B**) obtained with multiplanar reformation and in axial views (**C**,**D**). The patient underwent right nephrectomy for the primary tumor (clear cell RCC) (**A**,**B**) and was medically treated with a flat dose of nivolumab (480 mg/4 weeks) after he developed the secondary adrenal lesion. CT images before medical therapy showed the presence in the right adrenal gland of an inhomogeneous hypodense metastatic lesion with irregular margins (**C**, black arrow) that revealed a 32% decrease in size (28 mm vs. 19 mm) after medical treatment (**D**, black arrow) reflecting a partial response according to iRECIST (Table 2).

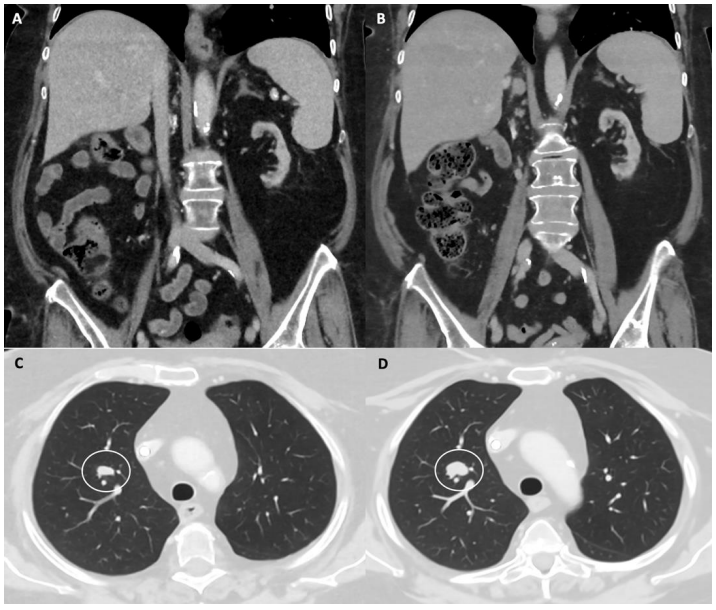

Figure 3. CT scans in a female patient, 80 years old with metastatic RCC in the right lung before (**A**,**C**) and after medical treatment (**B**,**D**). CT images are reported in coronal views (**A**,**B**) obtained with multiplanar reformation and in axial views (**C**,**D**). The patient underwent right nephrectomy for the primary tumor (clear cell RCC) (**A**,**B**) and was medically treated initially with a flat dose of nivolumab (480 mg/4 weeks). CT images before medical therapy showed the presence of a lung nodule in the superior right lobe (**C**, white circle) that showed a 60% increase in size (10 mm vs. 16 mm) after medical treatment (**D**, white circle) reflecting an immune-unconfirmed progressive disease according iRECIST (Table 2).

3.3. Combined Treatment Using Antiangiogenic and ICIs Drugs

As previously stated, several combination treatment regimens based on antiangiogenic and ICIs drugs have shown effectiveness in RCC, such as axitinib plus pembrolizumab as well as axitinib plus avelumab [11,36]. In particular, the use of combined treatment protocols opens new potential imaging response criteria which are currently under investigation and require to be systematically evaluated. Of note, in such cases the imaging evaluation usually follows standard RECIST when clinical trials are performed to assess the overall survival and PFS. However, since atypical responses of these novel drugs as well as their cytostatic effect may occur, the new imaging criteria are indirectly helpful in clinical trials, even though not completely included. In detail, Rini et al. reported that patients with metastastic RCC in treatment with pembrolizumab plus axinitib in clinical stable condition with unconfirmed disease progression by imaging, could continue the combined therapy until progression is confirmed by imaging at least 4 weeks later [11]. Similarly, Motzer et al. reported that patients with metastatic RCC in treatment with avelumab plus axitinib may continue the therapy although PD is demonstrated by imaging using RECIST, since they have no signs or symptoms of clinical progression [36]. These recent clinical experiences suggest that also combined treatment regimens in patients with metastatic RCC need not only the dimensional assessment of tumor lesions status to accurately assess cancer response (RECIST), but probably also other tumor features.

4. Prognostic Evaluation in Metastatic RCC Using Antiangiogenic Therapies

In clinical practice there is a significant need to identify early which patients may benefit from antiangiogenic agents, in order to avoid unnecessary side effects and to allow an early change of the chosen therapeutic agent. In particular, to assess the response prediction of antiangiogenic drugs, perfusion imaging techniques play a leading role; however, few experiences report the correlation between perfusion imaging parameters and prognosis. In detail, Fournier et al. found that responder patients to antiangiogenic treatment showed higher baseline values of blood flow and blood volume rather than patients with stable perfusion parameters during follow-up [37]. Furthermore, a >50% tumor blood flow decrease after the first cycle of treatment has been demonstrated to be correlated with a higher median overall survival compared with a <50% tumor blood flow decrease (20 months vs. 13 months) [37]. Furthermore, Flaherty et al. evaluated the changes of perfusion parameters using DCE-MRI in metastatic RCC patients before and after treatment with sorafenib. They found that the percent decline in K_{trans} (the rate of contrast material leakage from the intravascular space into the extracellular space) was significantly associated with PFS. In particular, they found that elevated baseline K_{trans} predicted favorable response, even though it was expected as a poor prognosis factor, identifying patients who can have the greatest benefit from antiangiogenic drugs [38]. Therefore, perfusion CT and MRI parameters may prove to be non-invasive biomarkers of prognosis, but their role in clinical practice has not been clearly defined yet [5]. Similarly, mCHOI criteria are able to assess response to antiangiogenic therapies better than RECIST and CHOI criteria, they also correlate better with the outcome (PFS and overall survival) [26]. In particular, mCHOI criteria accurately identify patients with PR and SD as patients with a long or short time to progression (448 days vs. 89 days), respectively ($p = 0.002$) [39]. Of note, the addition of texture analysis in the assessment of treatment response might improve the prediction response to antiangiogenic therapies in metastatic RCC patients. In this regard, Goh et al. assessed contrast-enhanced CT texture parameters of 87 metastases at baseline and during treatment: they observed that the decrease of tumor entropy and the increase of tumor uniformity were independent predictors of time to progression and potential predictive imaging biomarkers of response [40]. Thus, new advanced techniques to quantitatively assess images may be considered for this purpose, but additional investigations are needed to confirm these preliminary results.

5. Prognostic Evaluation in Metastatic RCC Using Immune Checkpoint Inhibitors

To date, only few patients have shown significant response to immunotherapies; these treatments are expensive and not free of important side effects. Hence, the identification of effective and prognostic biomarkers, preferably non-invasive, that can be used in clinical routine to select patients who benefit from ICIs, is desirable. In the literature, few studies are available about prognostic response evaluation of ICIs in patients with metastatic RCC. For example, the assessment of percentage of tumor infiltrating lymphocytes on histopathological samples correlates with immunotherapy response; a higher density correlates with a higher probability of response [41]. Few imaging prognostic biomarkers have been currently investigated. In particular, Sun et al. used CT images and RNA sequences of patients treated with ICIs to develop a radiomic signature of CD8+ T cells [42]. As well as for tumor infiltrating lymphocytes on histopathological samples, a higher baseline radiomics score correlates with a higher proportion of early objective response (3 and 6 months). In detail, the median overall survival was 24.3 months in patients with high radiomics score, while 11.5 months in those with a low score. Furthermore, Khene et al. built an artificial intelligence algorithm based on radiomics parameters extracted from pre-treatment enhancement-CT to predict tumor response in 48 metastatic RCC patients treated with nivolumab [21]. Five features were selected, and their four predictive models show high accuracy scores (K-nearest neighbor: 0.82; random forest tree: 0.7; logistic regression: 0.91; support vector machine: 0.81). In particular, their best model may predict response in >90% of patients: radiomics of pre-therapy imaging can accurately recognize responder patients. Hence, cancer immunotherapy is becoming one of the most promising cancer treatments, but only some patients benefit from it, so that the selection of these is one of the major future clinical challenges. Radiogenomics may aid clinicians to choose the most appropriate drug, being able to predict the therapy response as well as helping the oncologist to anticipate therapeutic decisions in no-responder patients to ICIs.

6. Conclusions

Advanced medical treatments, mainly consisting of antiangiogenic and ICIs drugs, have replaced the cytokine-based therapy in metastatic RCC. The availability of these innovative agents with predominant cytostatic effect makes conventional RECIST insufficient to get an adequate response imaging evaluation. Therefore, new imaging criteria have been proposed consisting of an mCHOI system in case of antiangiogenic treatment or iRECIST for ICIs agents; these new imaging criteria reflect more accurately tumor response. Furthermore, preliminary experience suggests that radiomics may be a potential tool to predict tumor response using ICIs in metastatic RCC. Additional multicenter prospective studies and clinical trials are necessary to confirm the clinical implications of either new imaging criteria or radiomics.

Author Contributions: Conceptualization and Supervision, S.M.; Writing—original draft preparation, M.C.; Writing—review and editing, V.R., A.S. and C.B.; visualization, G.D.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Padala, S.A.; Barsouk, A.; Thandra, K.C.; Saginala, K.; Mohammed, A.; Vakiti, A.; Rawla, P.; Barsouk, A. Epidemiology of renal cell carcinoma. *World J. Oncol.* **2020**, *11*, 79–87. [CrossRef] [PubMed]
2. Silverman, S.G.; Israel, G.M.; Herts, B.R.; Richie, J.P. Management of the incidental renal mass 1. *Radiology* **2008**, *249*, 16–31. [CrossRef] [PubMed]

3. Hsieh, J.J.; Purdue, M.P.; Signoretti, S.; Swanton, C.; Albiges, L.; Schmidinger, M.; Heng, D.Y.; Larkin, J.; Ficarra, V. Renal cell carcinoma. *Nat. Rev. Dis. Prim.* **2017**, *3*, 17009. [CrossRef]
4. Janzen, N.K.; Kim, H.L.; Figlin, R.A.; Belldegrun, A.S. Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. *Urol. Clin. N. Am.* **2003**, *30*, 843–852. [CrossRef]
5. Brufau, B.P.; Cerqueda, C.S.; Villalba, L.B.; Izquierdo, R.S.; González, B.M.; Molina, C.N. Metastatic renal cell carcinoma: Radiologic findings and assessment of response to targeted antiangiogenic therapy by using multidetector CT. *Radiographics* **2013**, *33*, 1691–1716. [CrossRef]
6. Lombardi, G.; Zustovich, F.; Donach, M.; Dalla Palma, M.; Nicoletto, O.; Pastorelli, D. An update on targeted therapy in metastatic renal cell carcinoma. *Urol. Oncol. Semin. Orig. Investig.* **2012**, *30*, 240–246. [CrossRef]
7. Motzer, R.J.; Hutson, T.E.; Glen, H.; Michaelson, M.D.; Molina, A.; Eisen, T.; Jassem, J.; Zolnierek, J.; Maroto, J.P.; Mellado, B.; et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: A randomised, phase 2, open-label, multicentre trial. *Lancet Oncol.* **2015**, *16*, 1473–1482. [CrossRef]
8. Cuenod, C.A.; Fournier, L.; Balvay, D.; Guinebretière, J.M. Tumor angiogenesis: Pathophysiology and implications for contrast-enhanced MRI and CT assessment. *Abdom. Imaging* **2006**, *31*, 188–193. [CrossRef]
9. Jonasch, E.; Gao, J.; Rathmell, W.K. Renal cell carcinoma. *BMJ* **2014**, *349*. [CrossRef]
10. Shinagare, A.B.; Krajewski, K.M.; Braschi-Amirfarzan, M.; Ramaiya, N.H. Advanced renal cell carcinoma: Role of the radiologist in the era of precision medicine. *Radiology* **2017**, *284*, 333–351. [CrossRef] [PubMed]
11. Rini, B.I.; Plimack, E.R.; Stus, V.; Gafanov, R.; Hawkins, R.; Nosov, D.; Pouliot, F.; Alekseev, B.; Soulières, D.; Melichar, B.; et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N. Engl. J. Med.* **2019**, *380*, 1116–1127. [CrossRef]
12. De Velasco, G.; Bex, A.; Albiges, L.; Powles, T.; Rini, B.I.; Motzer, R.J.; Heng, D.Y.C.; Escudier, B. Sequencing and combination of systemic therapy in metastatic renal cell carcinoma. *Eur. Urol. Oncol.* **2019**, *2*, 505–514. [CrossRef]
13. Dromain, C.; Beigelman, C.; Pozzessere, C.; Duran, R.; Digklia, A. Imaging of tumour response to immunotherapy. *Eur. Radiol. Exp.* **2020**, *4*, 1–15. [CrossRef]
14. Xiang, R.; Lode, H.N.; Gillies, S.D.; Reisfeld, R.A. T cell memory against colon carcinoma is long-lived in the absence of antigen. *J. Immunol.* **1999**, *163*, 3676–3683.
15. Motzer, R.J.; Escudier, B.; McDermott, D.F.; George, S.; Hammers, H.J.; Srinivas, S.; Tykodi, S.S.; Sosman, J.A.; Procopio, G.; Plimack, E.R.; et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N. Engl. J. Med.* **2015**, *373*, 1803–1813. [CrossRef]
16. Vig, S.V.L.; Zan, E.; Kang, S.K. Imaging for metastatic renal cell carcinoma. *Urol. Clin. N. Am.* **2020**, *47*, 281–291. [CrossRef]
17. Eisenhauer, E.A.; Therasse, P.; Bogaerts, J.; Schwartz, L.H.; Sargent, D.; Ford, R.; Dancey, J.; Arbuck, S.; Gwyther, S.; Mooney, M.; et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur. J. Cancer* **2009**, *45*, 228–247. [CrossRef] [PubMed]
18. Liu, Y.; Litière, S.; De Vries, E.G.; Sargent, D.; Shankar, L.; Bogaerts, J.; Seymour, L. The role of response evaluation criteria in solid tumour in anticancer treatment evaluation: Results of a survey in the oncology community. *Eur. J. Cancer* **2014**, *50*, 260–266. [CrossRef]
19. Gillies, R.J.; Kinahan, P.E.; Hricak, H. Radiomics: Images are more than pictures, they are data. *Radiology* **2016**, *278*, 563–577. [CrossRef] [PubMed]
20. Stanzione, A.; Ricciardi, C.; Cuocolo, R.; Romeo, V.; Petrone, J.; Sarnataro, M.; Mainenti, P.P.; Improta, G.; De Rosa, F.; Insabato, L.; et al. MRI radiomics for the prediction of fuhrman grade in clear cell renal cell carcinoma: A machine learning exploratory study. *J. Digit. Imaging* **2020**, *33*, 879–887. [CrossRef]
21. Khene, Z.-E.; Mathieu, R.; Peyronnet, B.; Kokorian, R.; Gasmi, A.; Khene, F.; Rioux-Leclercq, N.; Kammerer-Jacquet, S.F.; Shariat, S.; Laguerre, B.; et al. Radiomics can predict tumour response in patients treated with Nivolumab for a metastatic renal cell carcinoma: An artificial intelligence concept. *World J. Urol.* **2020**, 3–5. [CrossRef]
22. Han, K.S.; Jung, D.C.; Choi, H.J.; Jeong, M.S.; Cho, K.S.; Joung, J.Y.; Seo, H.K.; Lee, K.H.; Chung, J. Pretreatment assessment of tumor enhancement on contrast-enhanced computed tomography as a potential predictor of treatment outcome in metastatic renal cell carcinoma patients receiving antiangiogenic therapy. *Cancer* **2010**, *116*, 2332–2342. [CrossRef] [PubMed]
23. Baccala, A.; Hedgepeth, R.; Kaouk, J.; Magi-Galluzzi, C.; Gilligan, T.; Fergany, A. Pathological evidence of necrosis in recurrent renal mass following treatment with sunitinib. *Int. J. Urol.* **2007**, *14*, 1095–1097. [CrossRef]
24. Smith, A.D.; Lieber, M.L.; Shah, S.N. Assessing tumor response and detecting recurrence in metastatic renal cell carcinoma on targeted therapy: Importance of size and attenuation on contrast-enhanced CT. *Am. J. Roentgenol.* **2010**, *194*, 157–165. [CrossRef]
25. Choi, H.; Charnsangavej, C.; Faria, S.C.; Macapinlac, H.A.; Burgess, M.A.; Patel, S.R.; Chen, L.L.; Podoloff, D.A.; Benjamin, R.S. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: Proposal of new computed tomography response criteria. *J. Clin. Oncol.* **2007**, *25*, 1753–1759. [CrossRef]
26. Thian, Y.; Gutzeit, A.; Koh, D.-M.; Fisher, R.; Lote, H.; Larkin, J.; Sohaib, A. Revised choi imaging criteria correlate with clinical outcomes in patients with metastatic renal cell carcinoma treated with sunitinib. *Radiology* **2014**, *273*, 452–461. [CrossRef] [PubMed]

27. Sabir, A.; Schor-Bardach, R.; Wilcox, C.J.; Rahmanuddin, S.; Atkins, M.B.; Kruskal, J.B.; Signoretti, S.; Raptopoulos, V.D.; Goldberg, S.N. Perfusion MDCT enables early detection of therapeutic response to antiangiogenic therapy. *Am. J. Roentgenol.* **2008**, *191*, 133–139. [CrossRef]
28. Goh, V.; Ng, Q.S.; Miles, K. Computed tomography perfusion imaging for therapeutic assessment: Has it come of age as a biomarker in oncology? *Investig. Radiol.* **2012**, *47*, 2–4. [CrossRef]
29. Wolchok, J.D.; Hoos, A.; O'Day, S.; Weber, J.S.; Hamid, O.; Lebbé, C.; Maio, M.; Binder, M.; Bohnsack, O.; Nichol, G.; et al. Guidelines for the evaluation of immune therapy activity in solid tumors: Immune-related response criteria. *Clin. Cancer Res.* **2009**, *15*, 7412–7420. [CrossRef]
30. Fujimoto, D.; Yoshioka, H.; Kataoka, Y.; Morimoto, T.; Hata, T.; Kim, Y.H.; Tomii, K.; Ishida, T.; Hirabayashi, M.; Hara, S.; et al. Pseudoprogression in previously treated patients with non–small cell lung cancer who received nivolumab monotherapy. *J. Thorac. Oncol.* **2019**, *14*, 468–474. [CrossRef]
31. Besse, B.; Ferrara, R.; Mezquita, L.; Texier, M.; Lahmar, J.; Audigier-Valette, C.; Tessonnier, L.; Mazieres, J.; Zalcman, G.; Brosseau, S.; et al. Hyperprogressive disease in patients with advanced non-small cell lung cancer treated with PD-1/PD-L1 inhibitors or with single-agent chemotherapy. *JAMA Oncol.* **2018**, *4*, 1543–1552. [CrossRef]
32. Champiat, S.; Dercle, L.; Ammari, S.; Massard, C.; Hollebecque, A.; Postel-Vinay, S.; Chaput, N.; Eggermont, A.; Marabelle, A.; Soria, J.C.; et al. Hyperprogressive disease is a new pattern of progression in cancer patients treated by anti-PD-1/PD-L1. *Clin. Cancer Res.* **2017**, *23*, 1920–1928. [CrossRef]
33. Nishino, M.; Giobbie-Hurder, A.; Gargano, M.; Suda, M.; Ramaiya, N.H.; Hodi, F.S. Developing a common language for tumor response to immunotherapy: Immune-related response criteria using unidimensional measurements. *Clin. Cancer Res.* **2013**, *19*, 3936–3943. [CrossRef]
34. Seymour, P.L.; Cancer, C.; Group, T.; Bogaerts, J.; Perrone, A.; Medicine, T.; Ford, R.; Trials, C.; Consulting, I.; Mead, B.; et al. iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol.* **2017**, *18*, e143–e152. [CrossRef]
35. Kataoka, Y.; Hirano, K. Which criteria should we use to evaluate the efficacy of immune-checkpoint inhibitors? *Ann. Transl. Med.* **2018**, *6*, 222. [CrossRef] [PubMed]
36. Motzer, R.J.; Penkov, K.; Haanen, J.; Rini, B.; Albiges, L.; Campbell, M.T.; Venugopal, B.; Kollmannsberger, C.; Negrier, S.; Uemura, M.; et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N. Engl. J. Med.* **2019**, *380*, 1103–1115. [CrossRef]
37. Fournier, L.S.; Oudard, S.; Thiam, R.; Trinquart, L.; Banu, E.; Medioni, J.; Balvay, D.; Chatellier, G.; Frija, G.; Cuenod, C.A. Metastatic renal carcinoma: Evaluation of antiangiogenic therapy with dynamic contrast-enhanced CT. *Radiology* **2010**, *256*, 511–518. [CrossRef] [PubMed]
38. Flaherty, K.T.; Rosen, M.A.; Heitjan, D.F.; Gallagher, M.L.; Schwartz, B.; Schnall, M.D.; O'Dwyer, P.J. Pilot study of DCE-MRI to predict progression-free survival with sorafenib therapy in renal cell carcinoma. *Cancer Biol. Ther.* **2008**, *7*, 496–501. [CrossRef] [PubMed]
39. Nathan, P.D.; Vinayan, A.; Stott, D.; Juttla, J.; Goh, V. CT response assessment combining reduction in both size and arterial phase density correlates with time to progression in metastatic renal cancer patients treated with targeted therapies. *Cancer Biol. Ther.* **2010**, *9*. [CrossRef] [PubMed]
40. Goh, V.; Ganeshan, B.; Nathan, P.; Juttla, J.K.; Vinayan, A.; Miles, K.A. Assessment of response to tyrosine kinase inhibitors in metastatic renal cell cancer: CT texture as a predictive biomarker. *Radiology* **2011**, *261*, 165–171. [CrossRef]
41. Romagnoli, G.; Wiedermann, M.; Hübner, F.; Wenners, A.; Mathiak, M.; Röcken, C.; Maass, N.; Klapper, W.; Alkatout, I. Morphological evaluation of tumor-infiltrating lymphocytes (TILs) to investigate invasive breast cancer immunogenicity, reveal lymphocytic networks and help relapse prediction: A retrospective study. *Int. J. Mol. Sci.* **2017**, *18*, 1936. [CrossRef] [PubMed]
42. Sun, R.; Limkin, E.J.; Vakalopoulou, M.; Dercle, L.; Champiat, S.; Han, S.R.; Verlingue, L.; Brandao, D.; Lancia, A.; Ammari, S.; et al. A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: An imaging biomarker, retrospective multicohort study. *Lancet Oncol.* **2018**, *19*, 1180–1191. [CrossRef]