Published in final edited form as:

Abdom Radiol (NY). 2018 September ; 43(9): 2213–2220. doi:10.1007/s00261-018-1663-4.

Society of Abdominal Radiology disease-focused panel on renal cell carcinoma: update on past, current, and future goals

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Abstract

The disease-focused panel (DFP) program was created by the Society of Abdominal Radiology (SAR) as a mechanism to “improve patient care, education, and research” in a “particular disease or a particular aspect of a disease”. The DFP on renal cell carcinoma (RCC) was proposed in 2014 and has been functional for 4 years. Although nominally focused on RCC, the scope of the DFP has included indeterminate renal masses because many cannot be assigned a specific diagnosis when detected. Since its founding, the DFP has been active in a variety of clinical, research, and educational projects to optimize the care of patients with known or suspected RCC. The DFP is utilizing multi-institutional and cross-disciplinary collaboration to differentiate benign from malignant disease, optimize the management of early stage RCC, and ultimately to differentiate indolent from aggressive cancers. Several additional projects have worked to develop a

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Conflict of interest Matthew Davenport: Royalties from Wolters Kluwer. Ivan Pedrosa: None. Zhen Wang: Unrelated stockholder in Nextstrat Inc. Andrew Smith: Unrelated: president of Radiostics LLC, president of and patents received and pending for Liver Nodularity LLC, president of and patents received and pending for eRadioMetrics LLC, presidents of and patents received and pending for Color Enhanced Detection LLC. Hersh Chandarana: Unrelated hardware and software support from Siemens Healthcare. Ankur Doshi: None. Atul Shinagare: Unrelated consultant to Arog Pharmaceuticals and research funding with GTx Inc. Erick Remer: None. Sam Kaffenberger: None. Nicole Curci: None. Shane Wells: None. Stuart Silverman: None.

quantitative biomarker that predicts metastatic RCC response to anti-angiogenic therapy. While disease focus is the premise by which all DFPs are created, it is likely that in the future the RCC DFP will need to expand or create new panels that will focus on other specific aspects of RCC—a result that the program’s founders envisioned. New knowledge creates a need for more focus.

Keywords

Renal mass; Society of Abdominal Radiology; Disease-focused panel; Renal cancer; Renal cell carcinoma

Overview

The disease-focused panel (DFP) program was created by the Society of Abdominal Radiology (SAR) in the first year of the Society’s existence (2012), which resulted from a merger between the Society of Gastrointestinal Radiologists (SGR) and the Society of Uroradiology (SUR). The newly formed Society aimed to have its mission and members maintain a gastrointestinal or genitourinary focus and to develop disease-based expertise [1]. The DFP program was designed to support these goals by improving “patient care, education, and research” in a “particular disease or a particular aspect of a disease”. The renal cell carcinoma (RCC) DFP was among the first DFPs to form.

Requisites of the DFP program are that each panel conduct collaborative research between diverse members from multiple institutions who have expertise in the DFP’s focus [1]. Single-site studies generally suffer from lesser power, lesser generalizability, and greater group-think. The diverse network inherent to all DFPs facilitates multi-site collaboration, camaraderie, idea sharing, and network building. Cross-disciplinary collaboration is afforded by the mandatory inclusion of a non-radiologist member in every panel (in our case, a urologist), who provides key clinical insight into research design and general strategy [1].

Although the RCC DFP experienced “early wins” [2], there have been roadblocks. A major challenge facing all DFPs is inter-institutional sharing of image data. Inability to readily share images has stymied multiple proposals. Fortunately, the SAR Board and DFP oversight committee are actively working to address this. Another challenge has been transforming new ideas into completed projects. The initial DFP roster was enriched with senior radiologists who served the important roles of knowing the field, creating ideas, and advising research methodology. However, each DFP must be balanced with junior members who have time to execute project designs. Without people to do the work, great ideas go nowhere. The DFP accomplished this balance by introducing a structure to facilitate mentoring of all new members so they can lead multi-institutional projects of their own under the guidance of senior members. This mechanism aligns the interests of new members (i.e., professional development, relationship building, practical experience) with the interests of the DFP (i.e., publications, creation of new knowledge, advancing care of patients with renal masses) [1], and has accelerated its productivity.

In this summary, the formation, administration, challenges, accomplishments, and ongoing projects of the RCC DFP are reviewed. The panel hopes this review will stimulate reader

interest in the RCC DFP's mission, provide a roadmap for newer DFPs to see what strategies have worked and failed, and to establish future check-points for DFPs to follow.

Origins, administrative structure, initial plans, and early challenges

As one of the inaugural DFPs, the RCC DFP application was approved by the DFP oversight committee [1] in 2014 and its first in-person meeting was held at SAR in 2015. The initial panel consisted of 11 radiologists and 1 urologist from 11 academic institutions, each of whom had an established academic portfolio in RCC. Two co-chairs submitted the initial application. The stated mission was "to advance the radiologic contributions to the diagnosis and management of both localized and advanced renal cell carcinoma". The DFP had the following stated goals:

1. *Clinical practice* "Improve clinical practice through the development of new clinical-indication-based standardized imaging protocols and the development of new clinical-indication-based structured radiology reports."
2. *Education* "Educate radiologists and non-radiologists on the role of imaging in the management of suspected, localized, and advanced renal cell carcinoma."
3. *Research Aim 1* "Develop and validate non-invasive methods to assess the biologic behavior of renal cell carcinoma and to discriminate aggressive from indolent cancers."
4. *Research Aim 2* "Compare and validate image-based criteria for the assessment of treatment response in advanced renal cell carcinoma."
5. *Research Aim 3* "Develop a multi-institutional database and image repository for evaluating the natural history of renal cell carcinoma and the role of active surveillance."

To meet these goals, project leaders were identified to lead specific clinical, education, and research projects. Foundational projects included: (1) "Develop standardized imaging protocols based on clinical indication", (2) "Develop structured reports based on clinical indication", (3) "Evaluate variability of imaging protocols in evaluation of renal cancers", (4) "Evaluate impact of standardized structured reporting in management of renal cancer", (5) "Develop and validate the image-based assessment of biologic behavior of solid and cystic renal neoplasms", (6) "Create a multi-institutional database for evaluating the natural history of untreated renal neoplasms", and (7) "Compare image-based criteria for the assessment of treatment response in advanced RCC."

Although these goals and planned projects were worthwhile, it soon became clear that some of the projects were too ambitious and not feasible in the short term. The major barriers were a shortage of labor, sub-optimal short-term feasibility, and lack of infrastructure. For example, our ability to evaluate image-based criteria for treatment response and to study the natural history and biologic behavior of renal neoplasms each required the creation of an expensive multi-institutional database that could be viewed and analyzed by each member institution in an IRB-approved, HIPPA-compliant way. Such a database would require funding to support. Therefore, early efforts were refocused on less resource-intensive

projects while advocating to the SAR oversight committee that an image-sharing network was needed for all DFPs. Simultaneous with this advocacy, one panel member applied for extramural funding. To address the rate-limiting mismatch between idea generation and available members to execute the projects, the panel was expanded to include 4 new members, with each being asked to propose and lead specific projects. The current roster includes 16 members (15 radiologists and 1 urologist).

Early successes

Early successes included developing a collectively derived set of renal mass CT and MR imaging protocols [3, 4], studying renal mass reporting preferences [5] and reporting patterns [6] in multi-institutional samples, and pursuing multi-institutional grant funding for the assessment of vascular tumor burden as a predictor of RCC treatment response [7, 8]. Below is a summary description of each of these efforts.

Standardized CT and MR imaging protocols

A high-quality imaging examination is essential to accurately characterize indeterminate renal masses and to stage and surveil RCC [9, 10]. Our goal was to recommend standardized CT [3] and MR [4] imaging protocols that contain elements essential for an accurate diagnosis in a set of specific clinical scenarios (i.e., indeterminate renal mass characterization, pre-surgical or pre-ablation planning, post-nephron-sparing therapy surveillance, and post-nephrectomy and systemic therapy surveillance) that can be practically implemented across different institutions and practices. In addition to their use in clinical care, these imaging protocols will contribute to the DFP's goal of facilitating multi-institutional investigations of renal mass imaging.

The project began with codifying and reviewing CT and MR imaging protocols from each of the RCC DFP member institutions. The protocols varied substantially (e.g., number of post-contrast phases, imaging planes, MRI pulse sequences), further highlighting the need for standardization. Some of the variation reflected different opinions about how to balance innovative diagnostic strategies (e.g., use of contrast material dynamics to predict renal mass subtype [11]) with radiation exposure, while other variation reflected differences in institutional legacy, personal preferences, and lack of a clear standard. The standardized DFP protocols were developed by identifying key essential elements common to all of the members' institutional renal mass protocols, and then modifying them based on evidence. Where evidence was not available, the panel's collective expertise was derived through iterative consensus. The resultant protocols [3, 4] are available on our website [12] and include both essential and optional elements for each imaging indication. The protocols will be updated as new evidence becomes available.

Radiologist reporting and creation of a standardized template

There is a growing body of literature showing that disease-focused structured radiology reports are valuable and contribute to patient care [13–15]. Therefore, the DFP was motivated to create a standardized reporting template for indeterminate renal masses. Although there are some renal mass imaging features that most would agree are mandatory

to include in a radiology report (e.g., presence of mass enhancement and the presence of fat [5, 9]), many others are debatable (e.g., mass signal intensity on T2-weighted imaging [16], inclusion of Nephrometry scoring [17]). Prior to creating a recommendation for how masses should be reported, it was important first to collect necessary background information in two ways: (1) solicit opinions of urologists and radiologists regarding what belongs in such a report [5], and (2) measure what actually is reported by practicing radiologists [6]. This multi-institutional work [5, 6] led to the following conclusions. First, radiologists and urologists agree on some major points, but disagree on many others [5]. For example, urologists in general are not in favor of radiologists making management recommendations [5]. Second, radiologists often fail to report features [6] that urologists and (ironically) radiologists believe are essential for patient care [5]. These data indicate a need for standardized reporting of renal masses, and the DFP is actively working on addressing that. Once finished, it will be available for general use.

Vascular tumor burden and pursuit of national funding

A quantitative biomarker that can predict metastatic RCC response to anti-angiogenic therapy is needed to guide therapy; plan adaptive-design clinical trials; and avoid unnecessary increases in tumor burden, drug toxicities, and costs from ineffective treatment. Using the RCC DFP as a foundation, a multi-institutional, multi-disciplinary team was convened to optimize a quantitative CT imaging biomarker (i.e., “vascular tumor burden”) that could predict response of metastatic RCC to anti-angiogenic therapy [7]. This work led to the conception of a multi-institutional validation study using data from 12 completed prospective phase III clinical trials of subjects with metastatic RCC treated with various anti-angiogenic agents. Such a validation study would require (1) a software platform that could measure vascular tumor burden (already developed [8]), (2) image and data transfer mechanisms from the industry partners that sponsored the trials to the participating sites (logistics still being enumerated), and (3) extramural funding (not yet obtained). An NIH U01 grant was submitted and scored well but was not funded. A resubmission is planned.

Accelerating the research mission

The work of the DFP is accelerating. New members are exploring the effect of percutaneous tumor ablation on renal function, and the repeatability and meaning of texture analyses in renal masses—both study designs are multi-institutional. A three-stage multi-institutional Delphi method is being used to derive a novel renal mass lexicon designed to improve communication and standardization, akin to what has been created for liver imaging [18]. A recently published MRI algorithm [19] for the prediction of RCC subtype is undergoing multi-institutional validation. Lastly, the significance of homogeneous renal masses measuring 21–39 HU at contrast-enhanced CT [20] is being explored to determine if such masses require further follow-up. Below is a summary description of these research efforts.

Risk of contrast-induced nephropathy during percutaneous tumor ablation

The method by which treatment success is confirmed following renal ablation varies between providers and across institutions [21, 22]. Administering IV contrast material and imaging immediately after the ablation is executed (i.e., during the procedure) assists in

identifying residual tumor and permits immediate retreatment. It is unclear whether the administration of contrast material in this setting may impart a 'double-hit' phenomenon in which the nephron loss of ablation is exacerbated by the potential nephrotoxicity of contrast material [23]. The DFP will explore if administration of a standard intra-procedural dose of iodinated contrast material predicts medium- or long-term renal function impairment.

Repeatability and meaning of texture analyses of renal masses

Texture analysis has emerged as a potentially useful tool for the diagnosis and prognosis of renal masses. Prior studies have found that texture features can help characterize renal masses, predict tumor grade, and predict response to targeted therapy [24–29]. Although the fundamental principle across texture analysis investigations is the evaluation of tumor heterogeneity using pixel data, there is variability in image acquisition techniques, type of segmentation, post-processing software (including commercial and locally developed), image filtration algorithms, and type of texture metrics analyzed [30]. Early studies have suffered from small sample sizes, lack of multi-institutional validation, and inadequate correction for multiple hypothesis testing. Given the wide range of variables involved, it is difficult for investigators to reproduce or compare results across centers. To better understand the impact of various software platforms on texture analysis outputs, a multi-institutional retrospective study using imaging data derived from a multi-institutional RCC repository is being performed. Data collection is complete and data analysis is underway. The goal is to measure the variability across sites and software packages, and to determine if there are key texture metrics that predict histologic grade.

Developing a renal mass lexicon

Accurate characterization of a renal mass is critical for diagnosis and management. However, the terminology and definitions used to describe the imaging features of renal masses is variable, leading to difficulties interpreting results and marked interobserver variability [31–33]. This has limited the ability of radiologists to provide consistent clinical interpretations or to conduct reproducible research that can be reliably compared and validated [32–35]. To address these needs, the RCC DFP is developing a renal mass lexicon that will standardize the terminology used in the imaging-based characterization of renal masses. The lexicon is being built using a systematic multi-stage modified Delphi technique with established methods [36–38]. At the time of this writing, the DFP is in the second of three planned rounds of consensus-building teleconferences and blinded questionnaires [36–38]. Upon completion, the product will be a consensus set of terminologies that can be used to promote consistency in the care of patients and the research of imaged renal masses.

Validation of an imaging algorithm to subtype RCC

Historically, the detection of fat and enhancement have been the two most important features to assess when evaluating a potentially solid mass by imaging. While the former is virtually diagnostic of angiomyolipoma (AML), the latter (in the absence of macroscopic fat) implies the mass may be neoplastic. However, solid masses also can be benign tumors (e.g., oncocytoma, fat poor AML) or benign mimics (e.g., focal infection or inflammation) [39–42], or low-risk malignancies unlikely to affect a patient's lifespan [43]. Other than diagnosing AML by the identification of macroscopic fat, there has been no reliable imaging

method to distinguish benign from malignant masses with imaging alone. The concern that a solid mass may be malignant has led to unnecessary surgery for a benign diagnosis in approximately 20% of patients [43, 44], contributing substantial morbidity and shortened long-term survival due to loss of functional renal parenchyma [45, 46]. While percutaneous biopsies have the potential to reduce the number of unnecessary nephrectomies, they are not widely disseminated into clinical practice, perhaps due to variably stated diagnostic rates or concern for post-biopsy complications [47].

More recently, multiple institutions have reported single-center retrospective studies suggesting that CT and MR can be used to diagnose previously indeterminate specific benign (e.g., fat poor AML) and malignant (e.g., clear cell RCC) diagnoses without need of percutaneous biopsy [48, 49]. MRI is particularly well suited to subtype renal masses given the lack of ionizing radiation that complicates multiphase CT, and the multiparametric data sets obtained in standard clinical examinations. For example, it has been shown that small enhancing renal masses with homogeneous low signal intensity on T2-weighted images exhibit slower growth (i.e., tumor doubling time > 2 years) and may be better candidates for active surveillance [16]. Others have explored whether an MRI-based likelihood score of clear cell RCC histology may better identify which patients are suitable for active treatment [49]. Though promising, much of this work has been single center with relatively small datasets, especially for uncommon histologic variants. If the results can be validated in a larger multi-institutional sample, it would provide greater validity for incorporating these techniques into routine clinical care. The DFP is actively pursuing a multi-institutional design to address these issues.

Significance of homogeneous renal masses 21–39 HU at contrast-enhanced CT

Since many renal masses are first detected on an imaging study performed for unrelated reasons [50, 51], the DFP is interested in exploring whether further testing can be avoided for certain masses that are currently considered indeterminate. Homogeneous renal masses that measure > 20 Hounsfield Units (HU) on portal venous-phase CT are frequently encountered in clinical practice and typically require expensive additional imaging for complete characterization [52]. However, it has been shown in single-center studies that homogeneous low-attenuation masses measuring 20–39 HU on portal venous-phase CT are generally cysts and very unlikely to be aggressive cancers [20]. If confirmed to be true in a multi-institutional sample, this has the potential to substantially reduce the number of masses deemed indeterminate and the subsequent need for more testing. The DFP is pursuing a validation study to address this.

Educational ventures

Although creation of new knowledge is the highest priority, the mission of the RCC DFP is critically linked to education. Without disseminated knowledge, care cannot improve. To this end, a number of educational ventures are underway. Data from published DFP-conducted studies [5, 6] are being used to create a nationally accepted standardized reporting template for indeterminate renal masses that can be used in general practice. Concepts derived from published imaging protocols [3, 4] are being summarized in review format to determine the

evidence base supporting them. The RCC DFP hosts a website [12] that links to DFP-generated renal mass imaging protocols [3, 4], a list of DFP projects, kidney cancer resources for patients and providers, and an RCC DFP-curated database summarizing key literature in renal mass imaging [53]. In addition, the 2019 SAR annual meeting will feature the first RCC DFP hands-on workshop: a 3-h interactive experience led by DFP members that will give meeting participants practical experience with cutting edge renal mass imaging strategies. Details of the DFP-curated literature database and hands-on workshop are below.

RCC DFP article database

The SAR envisioned that each DFP would maintain a curated database [53] containing key published manuscripts that could be used by new members to become quickly acquainted with important and historically relevant literature. After some work, a publicly accessible online database [53] that features published manuscripts was released in the following domains: (1) renal mass basics, (2) renal mass subtyping, (3) renal mass biopsy, (4) renal mass ablation, and (5) imaging in systemic therapy. Residents, fellows, general radiologists, urologists, and urologists (among others) looking for a renal mass imaging reference can refer to this repository and find high-yield information. No curated collection is complete, and there are many important articles not listed in this forum. This work-in-progress project attempts to balance the simplicity of a dense collection with the need for comprehensive information. Articles will be added periodically on an ad-hoc basis.

SAR: 2019: hands-on workshop

The inaugural RCC DFP hands-on workshop will premiere at the 2019 SAR annual meeting. It is being designed to address three fundamental knowledge gaps: (1) small renal cancers are being over-diagnosed and over-treated [54, 55], (2) small benign renal neoplasms are being underdiagnosed and treated unnecessarily [54, 55], and (3) radiologists have heterogeneous methods of analyzing and reporting renal masses that may contribute to the preceding problems [5, 6]. The style of the course will include hands-on experiential stepwise learning. Participants will review 25 challenging and informative cases hand-selected by the RCC DFP. Image review will be conducted through a virtual picture archiving and communications system (PACS) interface through the participants' own laptops or tablets. Each case will include 1–3 multiple choice questions highlighting the themes and goals of the course and will be followed by a short 2- to 5-min didactic explanation highlighting key teaching points. Participants will be given the opportunity to: (1) learn how to characterize challenging indeterminate renal masses and to use that information to minimize unneeded treatment, (2) understand what elements are essential and preferred when reporting a renal mass, and (3) apply novel imaging-feature-driven algorithms to discriminate benign from cancerous masses and predict renal cancer subtype histology.

Perspectives from the consultant urologist

Modern urologic guidelines for the management of small renal masses (e.g., American Urological Association [56]) have increasingly underscored the complex interactions of competing health risks with the management of these of-ten-indolent masses. From the

perspective of a urologic oncologist who often during patient counseling balances tangible cancer-related fears with the opaque intangible risks of intervention, any improvement in risk refinement by non-invasive means is inherently valuable. The DFP already has shown the ability to bolster the interpretation and communication of valuable imaging-based data to urologists via templated reports geared towards maximal clinical utility. Developments in the ability to assess disease aggressiveness and RCC subtype would be particularly valuable to improve individual risk–benefit assessments, and complete descriptions of renal anatomy (e.g., vascular) and tumor extent have the ability to enhance periprocedural patient safety. In general, advances in the ability of the practicing urologist to incorporate more nuanced and accurate estimates of risk will have a profound impact on individual treatment decisions (both active and surveillance-based), as well as population health and healthcare system resource utilization. Ultimately, the value of the DFP will depend on the generation and dissemination of generalizable knowledge that improves patient care across specialties.

Future directions and summary

Radiologists are vital in the care of patients with renal masses and the RCC DFP continues to advance our understanding and role in this setting. Growth of the DFP will bring new opportunities and new challenges. DFP recommendations and best-practices will increasingly benefit from cross-specialty collaboration, but this will encounter logistical and political hurdles. As was anticipated at the outset of the DFP program, other DFPs have grown beyond capacity and are splitting into smaller groups. ‘Spin-off’ DFPs that focus on a narrow unexplored aspect of RCC are likely to develop and the RCC DFP will work with them to build synergies and prevent overlap. Future efforts will take a more patient-centered approach. For example, renal mass reports have to date focused on the perspectives of radiologists and referring physicians. Patients now have access to radiology reports and likely would have valuable insights regarding how best to phrase certain findings or make certain recommendations. Determining better ways to differentiate indolent from aggressive masses and to report those differences in a coherent and standardized way are our major challenges in the years to come. It is hoped that the early challenges and successes of the DFP will lead to future work that fundamentally improves the care of patients with renal masses. SAR members who have published in this space are encouraged to contact the SAR [57] to express their interest in joining the panel.

Acknowledgements

We would like to thank all the members of the RCC DFP for their tireless work.

Funding No funding was solicited or used to support this work. This work has not been previously published.

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