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Collaborative Review: Factors Influencing Treatment Decisions for Patients with a Localized Solid Renal Mass.

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STRUCTURED ABSTRACT

CONTEXT

With the addition of active surveillance (AS) and thermal ablation (TA) to the urologist's established repertoire of partial (PN) and radical nephrectomy (RN) as first-line management options for localized renal cell carcinoma (RCC), appropriate treatment decision-making has become increasingly nuanced.

OBJECTIVE

To critically review the treatment options for localized, non-recurrent RCC; to highlight the patient, renal function, tumor and provider factors that influence treatment decisions; and to provide a framework to conceptualize that decision-making process.

EVIDENCE ACQUISITION: A collaborative critical review of the medical literature was conducted.

EVIDENCE SYNTHESIS

We identify three key decision points when managing localized RCC: (1) decision for surveillance versus treatment, (2) decision regarding treatment modality (TA, PN or RN), and (3) decision on surgical approach (open versus minimally invasive). In evaluating factors that influence these treatment decisions, we elaborate on patient, renal function, tumor and provider factors that either directly or indirectly impact each decision point. As current nomograms, based on pre-selected patient datasets, perform poorly in prospective settings, these tools should be used with caution. Patient decision aids are an underutilized tool in decision-making.

CONCLUSION

Localized renal cell carcinoma requires highly nuanced treatment decision-making, balancing patient and tumor specific clinical variables against indirect structural influences to provide optimal patient care.

Keywords: Renal Cell Carcinoma, Active Surveillance, Thermal Ablation, Partial Nephrectomy, Radical Nephrectomy, Patient Decision Aid, Nomogram

INTRODUCTION

Renal cell carcinoma (RCC) represents approximately 2% of all diagnosed cancers and is the 3th most common genitourinary malignancy following prostate and bladder cancer.[1,2] There are 403,000 new cases diagnosed worldwide annually, with the incidence of new RCC highest in North America and Western Europe.[2] The incidence of RCC continues to grow by approximately 2-3% each year, due in large part to the increased utilization of cross-sectional imaging. As such, the increased incidence in RCC is primarily driven by increased identification of incidentally detected, localized RCC. Therefore, an appropriate personalization of treatment intensity remains a key priority in urologic practice.[3]

Localized RCC, often defined as clinical T1-2N0M0 RCC, is a disease that has been historically managed with surgery. Historically, open radical nephrectomy (RN) remained the gold standard treatment modality since its seminal description by Robson for many decades, until the introduction of open partial nephrectomy (PN) following recognition of the benefits of nephron preservation. With advances in surgical technology, laparoscopic and robotic surgical approaches have largely eclipsed traditional open surgery for localized masses.[4-6] Additionally, clinical practice guidelines have expanded to endorse thermal ablative (TA) therapies - such as radiofrequency ablation (RFA) and cryoablation (CA) - as first-line treatment option.[7,8] Furthermore, active surveillance is now increasingly utilized for patients with small renal masses.[9-11]

While the number of treatment options for patients with clinically localized solid renal masses has increased, debate continues regarding the optimal strategy to personalize management.

Indeed, treatment decision-making for localized solid renal masses must balance several, often competing, priorities. These include oncologic efficacy, nephron preservation, treatment-related morbidity and treatment-related burden (Figure 1). In this collaborative review, we evaluate the key factors that contribute to critical clinical decision-making for patients with localized RCC.

EVIDENCE ACQUISITION

As established by prior collaborative reviews, the first and senior authors proposed a framework that was iteratively revised by all coauthors. A search of PubMed from inception until May 1, 2020 was performed for each topic using MeSH subject headings along with free-text, related, derivative, and exploded terms. MEDLINE, EMBASE, and Scopus were used to search the English literature from inception to May 2020 using the following terms: *''renal mass/tumor''* OR *"renal cell carcinoma", ''partial nephrectomy'', ''radical nephrectomy'', ''nephron-sparing surgery', "active surveillance", "ablation", "radiofrequency ablation",* OR *"cryoablation",* in conjunction with *"decision aid'', ''risk factors'', ''renal function'',* OR *''survival''.* The available data were synthesized qualitatively. The first and senior authors drafted this narrative review, which was critically revised by all coauthors. After a number of iterations, consensus regarding the content of the manuscript was reached among the authors. In the process of writing this critical review, the most recent pertinent studies were also added as references. Ultimately, while not a formal systematic review, we adhered to established journal guidelines for collaborative reviews of this nature.

EVIDENCE SYNTHESIS

We identified three key decision points that patients and clinicians face when managing localized RCC – specifically, (1) the decision for surveillance versus treatment, (2) the decision for treatment (TA, PN or RN), and (3) the surgical approach (open versus minimally invasive) to PN or RN (Figure 2). As we address the various factors that influence these decisions below, we specifically indicate which decision points are directly affected in the sub-section heading; each of the main decision points are summarized in Figures 3-4. However, as previously noted, not all of the below factors have a direct impact on treatment decision; for the individual patient and clinician, certain factors are of primary importance, while others are structural and may indirectly influence the ultimate decision. (Figure 1). All of these factors must be balanced against the goals of treatment to generate a patient-focused treatment plan.

Factors that Influence Treatment Decision

1. Patient Factors

1.1 Age

(Potential Influence on Decision Points: 1, 2, 3)

Patient age remains an important consideration in the decision for treatment for patients with localized RCC. AS with delayed intervention is a safe treatment option, especially for older patients, as the risk of metastatic progression in appropriately selected patients has been shown to be remote.[12-14] As for the choice of curative therapy, multiple studies have established the safety and efficacy of RN, PN and TA in older patients. [15-20]

Dovetailing with risks associated with biologic age is the notion of competing risks of mortality – the understanding that competing causes of death must be weighed against the benefit of RCC treatment to help make an informed decision to treat. In patients with localized RCC, age is the strongest predictor of mortality – and specifically, non-RCC related mortality.[21]

1.2 Race and Ethnicity

(Potential Influence on Decision Points: None)

While race, in close association with socioeconomic status, plays an important role in access to healthcare and subsequent treatment of all cancers, including localized RCC,[22,23] there are few data to support a unique treatment paradigm based on race alone. The only exception may be patients with suspected renal medullary carcinoma, a rare RCC histologic subtype almost exclusively found in young adults with sickle cell trait / hemoglobinopathies and of African descent, where upfront systemic therapy may be considered over immediate local treatment.[24]

1.3 Frailty & Performance Status

(Potential Influence on Decision Points: 1, 2, 3)

Frailty, a state of vulnerability to stressors, is increasingly recognized as an important predictor of cancer treatment outcomes, including genitourinary malignancies.[25] Yet, frailty is challenging to objectify as it represents a complex, multidimensional interplay between adaptive capacity and resiliency to stressors.[26] Although frailty is closely associated with age in the cancer population, cancer progression itself may contribute to

physiologic decline and increased frailty. Since frailty encompasses more than age or decline of a single organ-system, this metric may be a stronger predictor of postoperative outcomes and survival than prior surgical risk assessment tools, including performance status.[26] Current measures of frailty range from single-item assessments to composite scores comprised of up to 90 factors. Examples of frailty score objectification tools within the oncology space include the Phenotypic Frailty, the modified Frailty Index, and the Comprehensive Geriatric Assessment.[27-29] While no single tool has been validated and optimized for all patient populations, frailty evaluation is strongly recommended for patients older than age 70 and those with significant weight loss (>5%) because of chronic illness.[26,30]

As such, highly frail patients should be strongly considered for active surveillance or less aggressive treatment options such as ablation. If surgical intervention is warranted, and nephron-sparing surgery is not imperative, then radical nephrectomy via a minimally invasive approach should be strongly considered, especially for anatomically complex renal masses that may carry higher perioperative risks in patients undergoing NSS.[31] This population may represent an ideal opportunity for geriatric oncology evaluation.[32]

1.4 Comorbidity Status (Charlson Comorbidity Index, ASA)

(Potential Influence on Decision Points: 1, 2, 3)

Multiple studies have established comorbidity indices, such as the Charlson Comorbidity Index (CCI) and American Society of Anesthesiologist (ASA) physical status, as important predictors of treatment outcomes. In addition, CCI is also a major contributing risk factor to non-RCC mortality.[33] As such, patient comorbidity profile must be

integrated into treatment decision-making and potentially subsequent post-treatment surveillance.[34,35] Perioperative complications are significantly higher in patients with higher CCI scores,[36,37] but there is little data on the long-term impact of baseline comorbidity status following surgical treatment of localized renal masses. Independent of the impact of specific comorbidities on renal function (addressed later), AS or TA is favored in highly comorbid patients.[38]

It is also worth highlighting briefly two comorbid states not captured in the above metrics. First, in patients with a history of a prior malignancy or concurrent active malignancy, consideration should always be given to the possibility of metastatic disease to the kidney rather than a primary RCC. While rare for these lesions to be solitary, renal mass biopsy (RMB) can readily establish pathology and catalyze multi-disciplinary approach to management.[39] Second, in patients who are immunocompromised, outcomes of localized RCC treatment mirrors that of patients who are immunocompetent,[40-42] but data for safety of active surveillance are limited.[43]

1.5 Familial / Genetic syndromes

(Potential Influence on Decision Points: 1, 2)

While the focus of the review is on sporadic RCC, patients with a known hereditary kidney cancer, representing 5% of all RCC cases, may warrant modification to treatment and surveillance approaches.[44,45] Generally, referral for genetic evaluation is indicated in patients who are diagnosed before age 46,[46] have bilateral or multifocal tumors, ≥1 close relative with clear cell RCC or have a tumor with non-clear cell histology.[47]

As patients with hereditary RCC often present at a younger age with bilateral and/or multifocal tumors and are likely to develop additional sites of disease, the goals of management are not only complete surgical resection, but also an emphasis on maximal renal function preservation and appropriate calibration of surgical intervention.[48,49] Therefore, nephron sparing approaches, with an emphasis on enucleation, are recommended with maximal resection of all lesions in a single setting.[44] Subsequent management need to be highly individualized based on the syndrome and the patient's known tumor growth kinetics, size and location.[44,48] When considering the management of renal tumors in patients with genetic syndromes, it merits specific mention that patients with HLRCC require early, aggressive surgical resection at the time of diagnosis and may benefit from regional lymphadenectomy as well, as early metastatic progression is known to occur.[44,45,48]

1.6 Anticoagulation/Antiplatelet Agent dependence & Coagulopathy

(Potential Influence on Decision Points: 1, 2, 3)

Patient utilization of antithrombotic agents (ATAs), including anticoagulants (ACs) and antiplatelet agents (APAs), is a clinical factor that can strongly influence decision-making. It is important to note that utilization of aspirin 81 mg through surgical procedures, including PN, has not been associated with increased perioperative bleeding risk and can likely prevent serious cardiac events in patients with underlying vascular pathology, especially drug-eluting cardiac stents.[50,51] At the same time, continuation of APAs such as clopidogrel perioperatively has been associated with a significantly higher rate of bleeding complications (OR 2.19, 95% CI 1.06-4.51, p=0.03).[51] For this

reason, current guidelines recommend cessation or bridging of ATAs prior to RCC surgery and TA.[8,52-54] For procedures that carry a high risk of perioperative bleeding, these medications must also be resumed with caution.

Independent of bleeding risk, use of ATAs may often be considered as a surrogate marker of a patient's comorbidity status (i.e. related to the underlying diagnosis for which ATA is being prescribed). While there are established guidelines on perioperative management of ATAs,[52,54,55] the very fact that a patient is on an ATA should warrant reconsideration of treatment options. ACs are utilized for patients for atrial fibrillation, venous thromboembolic (VTE) disease and valvular heart disease and should be stopped 1-5 days prior to intervention, with or without bridging depending on risk of VTE. In contrast, APAs are typically utilized for patients with arterial disease and need to be stopped 5-7 days prior to intervention.[54] Cessation of anticoagulants is not without inherent risks and thus must be integrated into critical treatment decision-making.

Based on the above, patient use of ATAs should strongly be considered for AS in lieu of active treatment, if oncologically appropriate. For patients with recent synthetic valve placement for valvular heart disease, who require short-term (3-6 months) AC,[56,57] and in patients on APAs that cannot be stopped for 3-12 months (3 months for bare metal stents, 12 months for drug-eluting stents [DES]), AS with DI is an ideal management strategy. If delaying intervention is associated with increased risk of metastatic spread, then the treatment decision should be informed by the ability to continue ATA through treatment, the perioperative cessation period, the associated increased risk of VTE or thrombotic episodes, the risk of bleeding with early ATA resumption, and expected surgical recovery. In general, patients at high risk for VTE or thrombotic episodes should

be continued on therapy or bridged to minimize time off medications. In the EORTC 30904 randomized clinical trial, in the setting of a normal contralateral kidney, there was no difference in progression to ESRD in patients undergoing RN or PN.[58] Therefore, renal function permitting and if oncologically appropriate, patients at high risk for VTE or thrombotic episodes who are in need of intervention should be guided towards RN, due to decreased morbidity, quicker recovery, and lower risks of resuming anticoagulation soon after treatment.

1.7 Smoking status

(Potential Influence on Decision Points: 2)

Cigarette smoking is an established risk factor for RCC development, is associated with advanced stage disease at presentation and is independently associated with worse cancer-specific and overall survival.[59-64] However, smoking status, by itself, should not drive decisions regarding treatment modality, but should be considered in the context of perioperative risks. Active smoking (particularly within 1 year of surgical intervention) increased in-hospital mortality by 20% and major postoperative complications by 40%.[36,65] In contrast, smoking cessation, even in the short-term (4-8 weeks) before surgical intervention, was associated with 25-50% reduction in respiratory complications and 30% reduction in impaired wound healing, among other benefits.[65,66]

1.8 History of previous surgery

(Potential Influence on Decision Points: 1, 2, 3)

Prior surgery, either for RCC or other etiologies, impacts surgical approach. Patients with prior abdominal surgery or radiation, particularly in the upper quadrant of interest, may be best served by an open anterior approach (if only a transperitoneal approach is technically feasible) or retroperitoneal open/MIS approach if appropriate.[67,68] Of note, while patient and tumor factors may affect retroperitoneal or transperitoneal/anterior approach, multiple studies have demonstrated no significant difference in oncologic outcomes.[69] Similarly, prior intra-abdominal surgery or radiation may influence patients and providers to pursue TA and surveillance in appropriately selected patients.

1.9 Risk of COVID-19 morbidity

(Potential Influence on Decision Points: 1, 3)

In 2020, it is impossible to ignore the impact of the COVID-19 pandemic on cancer care and treatment decision-making. According to recent reports, perioperative mortality rates in COVID-positive patients are concerning, and COVID-19 is associated with significant pulmonary complications.[70] As we note below, surveillance for localized cT1-2 RCC is safe, and at the very least, 3-6 months delay does not appear to significantly impact outcome – hence, active treatment in SARS-CoV-2 positive patients or in geographical locations where risks of nosocomial COVID-19 infection are high should be deferred until competing risk of COVID morbidity is deemed acceptable.[71]

1.10 Patient preferences

While this topic has been relatively understudied, patient preferences and values regarding the goals of treatment play a key role in shared decision making. Moreover, in

some cases the patient's priorities for treatment (e.g., risk of CKD versus fear of recurrence), may differ from the clinician's prioritization of the goals of treatment.[72-77] Patient decision aids (discussed later) are starting to help address this deficiency.

2. Kidney Factors - Renal Function Considerations

2.1 Estimated (or measured) glomerular filtration rate

(Potential Influence on Decision Points: 1, 2)

Long-term preservation of kidney function is a critical consideration in the management of patients with localized renal cell carcinoma. Between 10-50% of patients with RCC have chronic kidney disease (CKD) prior to any treatment,[78,79] which may significantly influence therapeutic approach.

Even patients on AS can experience eGFR decline. Castaneda et al. demonstrated that, even in well-selected AS patients in the DISSRM cohort, nearly two-thirds of patients on AS experienced a decrease in eGFR and the annual eGFR decline (1.49±0.3 ml/min/1.73 m2) exceeded that expected from aging alone.[79,80]. Yet, forgoing invasive treatment clearly affords optimal prognosis with regard to renal preservation.

The EORTC 30904 study is the only prospective randomized study comparing different surgical treatment strategies for RCC.[58] In this cohort, where patients with normal renal function and renal masses 5cm or less in diameter were randomized to PN vs RN, PN was associated with significantly less “moderate” renal dysfunction (eGFR < 60), but there was no significant difference in advanced kidney disease (eGFR < 30), kidney failure (eGFR < 15) or overall survival when compared to patients who underwent RN. In this population of patients who were followed for a median of 6.7 years, moderate renal dysfunction was reached by 85.7% undergoing RN and 64.7% undergoing PN, underscoring the significant impact surgery has on kidney function.[81] Importantly, after the initial post-surgical eGFR decline, renal function was stable at a median follow up of ~7 years.[81] As such, while the impact of RN is undeniable, the clinical significance of a

lower eGFR in patients with normal contralateral kidneys is uncertain and may not be consequential.

When comparing the renal function outcomes of the 4 main treatment options – RN, PN, TA and AS, Hiten et al. again demonstrated that greatest decline in GFR stems from RN compared to other treatment modalities (15 ml/min/1.73m^2 less than PN; 10.3 ml/min/1.73m^2 less than TA; 10 ml/min/1.73m^2 less than AS). Meanwhile PN and TA have similar impact on eGFR.[82]

Recently, the concept of surgical CKD has been introduced, suggesting that surgically induced renal dysfunction may have a different long-term prognosis than medically induced CKD. Specifically, while the above interventions yield an immediate reduction in eGFR, a subsequent progressive decline in eGFR may reflect medical renal disease due to medical comorbidities.[82,83] Indeed, at least in patients with normal pre-operative renal function, eGFR reduction from surgical resection does not appear to affect patient life-expectancy / overall survival, as observed in the EORTC 30904 cohort.[58] Overall survival appears to correlate with eGFR decile below 45 ml/min/1.73m^2 ; however, predictive models for assessing risk of significant eGFR decline following renal surgery are based on small cohorts and are yet to be validated.[8,83-85] In sum, the risks of long-term harm related to CKD from surgical resection are controversial and must be thoughtfully balanced against immediate risks of more complex surgery, especially in the frail elderly with a normal contralateral kidney and an anatomically complex renal mass.[86]

2.2 Proteinuria

(Potential Influence on Decision Points: 1, 2)

Beyond baseline eGFR, early markers of CKD such as proteinuria should be considered during shared decision-making. O'Donnell et al., in their study of 1622 patients undergoing surgical treatment for localized RCC, noted that 18% of patients were overlooked as being at risk for CKD progression based on eGFR alone. Proteinuria was an independent predictor of renal function decline (RFD), with 3-year RFD rates ranging from 2.8% to 31.5% depending on magnitude of baseline proteinuria.[87] Therefore, initial evaluation of patients with localized RCC should include a urinalysis. Current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines combine baseline eGFR and proteinuria to define CKD, underscoring the importance of proteinuria as a known marker for the severity of CKD and a robust predictor of a patient's future renal function along with cardiovascular morbidity and mortality.[88]

2.3 Status of contralateral kidney

(Potential Influence on Decision Points: 1, 2)

A thorough evaluation of patients with localized RCC necessitates an appraisal of the status of the contralateral kidney. Congenital absence of the kidney is rare,[89] but if present, would render nephron sparing imperative in the solitary kidney with RCC. An atrophic kidney or one with minimal residual function (<10-20%) on NM renal scan or on parenchymal renal volume assessment with cross-sectional imaging would establish the RCC kidney as a functional solitary kidney, and similarly would require for nephron-sparing approaches to be prioritized.[90,91] In both these clinical scenarios, AS with

delayed intervention is recommended if feasible, although the threshold for treatment should prioritize nephron preservation.[31,92,93] RN should be utilized only if absolutely necessary, as this would render the patient dialysis-dependent.

2.4 Comorbidities associated with development or progression of chronic kidney disease (DM, HTN, Morbid Obesity, Recurrent Nephrolithiasis)

(Potential Influence on Decision Points: 1, 2)

In addition to baseline CKD, many patients who present with localized RCC harbor comorbidities that predispose or contribute to the development of CKD, including HTN, diabetes, heart disease, obesity, tobacco use and metabolic syndrome.[78,94-96]

As mentioned earlier, work by Lane, Campbell and colleagues suggests that surgically induced renal dysfunction is a distinct entity from medically induced CKD.[82,83] Compared to patients with surgical-CKD (CKD-S), patients with baseline medical CKD and superimposed surgical dysfunction (CKD-M/S) had higher rates of progressive decline in renal function, all-cause mortality, and non–renal cancer mortality (HR 1.69–2.33, all $p < 0.05$). Specifically, a post-operative eGFR < 45 ml/min/1.73 m2 predicted significantly worse outcomes. In this study, patients with CKD-M/S were more likely to have diabetes, HTN and heart disease as potential contributors to baseline CKD impairment.[83] As such, in patients without these medical comorbidities at risk for medical CKD, the concern for surgically-induced CKD alone may have less influence on treatment choice.

Therefore, even in patients with normal baseline eGFR, consideration should be given to future eGFR decline in patients with concomitant medical comorbidities. Treatment

modalities with less impact on renal function, specifically PN, TA and AS, should be favored over RN. Indeed, current guidelines specifically point to AS as an ideal treatment for patients with cT1a tumors and multiple medical comorbidities; in patients with larger tumors for which intervention is warranted, PN or TA is preferred over RN.[31]

3. Tumor Factors

3.1 Tumor size

(Potential Influence on Decision Points: 1, 2, 3)

Tumor size, characterized by clinical T-stage, remains a critical component contributing to treatment choice, reflecting data regarding the technical feasibility of PN versus RN based on tumor size. Indeed, current guidelines state that PN remains the standard of care for cT1a lesions (<4 cm). PN vs. RN for cT1b lesions should be used judiciously (4-7 cm), while RN is recommended over PN for cT2 lesions (>7 cm).[8,31,97] Recent studies have demonstrated feasibility of PN for cT2 lesions in highly select patient cohorts.[98,99] In a systematic review, Mir et al. note that in patients with cT2 lesions, despite having greater blood loss and perioperative complications, PN had comparable oncologic outcomes compared to RN.[99] However, while observational data suggest PN may be feasible in carefully selected patients, there remains an absence of high-quality, prospective data demonstrating oncologic non-inferiority for PN. So, while associated with greater morbidity, PN is possible and can be considered for larger renal masses in patients for whom this more complex surgery can be clinically justified (e.g. baseline renal function and anatomically favorable cT2 mass).

Thermal ablation success is heavily dependent on size and is primarily recommended for cT1a tumors.[7,8] For T1b tumors, while technically feasible in select patients, adjunctive maneuvers and multiple access sites are often required, higher rates of local recurrence are seen, and the procedures are associated with a higher complication rate. [100,101] Due to lack of high quality evidence, the EAU guidelines still strongly recommend surgical management of T1b or larger tumors over TA.

AS with delayed intervention is recommended for patients with small renal masses (<2 cm) and patients with significant comorbidities.[8,31,92] Based on the strength of prospective studies,[9-11] there are strong data to support the oncologic safety of AS for patients with cT1a and even cT1b-2 localized renal masses – with metastatic progression rates between 0-6% and CSM rates between 0-18%.[92,102] The key to AS success is delayed intervention and appropriate risk-stratification based on patient and tumor factors.

3.2 Anatomic complexity

(Potential Influence on Decision Points: 2, 3)

The impact of tumor anatomic complexity, as objectified by the various proposed nephrometry scoring systems, on risks of perioperative complications and thus on preoperative decision-making has been well documented and validated.[103,104] Similarly, in the setting of TA, the MC2 score and ABLATE algorithm provide similar guidance regarding risk of procedural complications, identify potential technical challenges and need for ancillary procedures.[7,105,106] Ultimately, while these tools provide a jumping off point for clinical decision-making, they should not be used in isolation to determine the best treatment. As noted by Beksac et al., although anatomic complexity does correlate with tumor grade and histology, it is imperfect at predicting achievement of oncologic success.[107]

3.3 Tumor Location (Anterior/posterior, Hilar)

(Potential Influence on Decision Points: 2, 3)

Independent of tumor complexity, a central/hilar tumor location has important implications for treatment choice. From a surgical perspective, centrally located tumors are more likely to require RN or open PN, particularly in patients with imperative indications for nephron-sparing approaches.[104,108] As it pertains to TA, centrally located tumors are also subject to a 'heat-sink effect' with diminished energy delivery to target tissue diminishing ablation – thereby often precluding use of TA and indicating need for either surgical intervention or AS.[105] However, this limitation may be more restricted to RFA rather than cryoablation.[105] All other factors being equal, a centrally located renal mass may lower the threshold to consider AS and DI, sparing patients a potentially morbid NSS or RN with associated renal impairment.

Similarly, an anterior/posterior tumor location has important implications for treatment choice. Posterior tumors are more amenable to percutaneous TA and retroperitoneal surgery,[67,105] while anterior tumors are best treated with transperitoneal approach. The anterior/posterior location has minimal impact on patients undergoing RN or AS.

3.4 Tumor growth patterns and kinetics

(Potential Influence on Decision Points: 1, 2, 3)

Tumor growth is not associated with the risk of malignancy, as (benign) oncocytomas may also demonstrate lesion growth.[109] Tumor growth kinetics should be incorporated into the decision for a patient to remain on AS or proceed to delayed intervention (DI), as it is a predictor for metastatic progression. While the mean linear growth rate (LGR) is 0.26-0.44 cm/year for all renal masses under surveillance, the mean LGR for patients undergoing intervention is significantly higher (0.62-0.73 cm/year).[92,102,110,111].

Because LGR has been associated with the risk of metastatic progression,[38,92] growth rates must be watched carefully. High LGR (>5 mm/yr) is a commonly used indication for renal biopsy and/or intervention.[112] Moreover, an infiltrative tumor growth pattern, in contrast to a well-circumscribed lesion, may point to more aggressive histology – and therefore favor more aggressive therapy.[113,114] In such cases, RN or wider margin PN may be preferred over enucleation, TA or AS.

3.5 Multifocality and Bilateral Renal Lesions

(Potential Influence on Decision Points: 1, 2, 3)

Approximately 2% of patients present with bilateral renal masses, while ~1-2% will develop contralateral metachronous renal tumors.[48,115,116] As in patients with genetic syndromes, the primary goal of management in these cases should be surgical resection balanced against renal function preservation and reduction of surgical morbidity. Staged PN for amenable masses, or primary PN of the smaller mass and staged RN of the larger mass, has been the mainstay of therapy.[31,117] However, recent series have demonstrated the feasibility of simultaneous PN in experienced hands.[118] In addition, TA or AS of smaller lesions may be considered.[119]

3.6 Adjunctive Pre-Treatment Testing: Renal Biopsy and Molecular Imaging

(Potential Influence on Decision Points: 1 & 2)

Approximately 30% of patients who undergo partial nephrectomy harbor benign tumors [120] Thus, percutaneous renal mass biopsy (RMB) can help reduce over-treatment in this patient population. RMB is a safe and effective technique to sample indeterminate

renal masses for which histology may impact treatment choice.[31,121] Nevertheless, patients in whom AS is the only treatment choice or in patients with long life-expectancy who are unenthusiastic about long-term surveillance, RMB's role is controversial.[122] While many of the authors routinely use RMB in clinical practice, RMB, outside of a clinical protocol setting, is usually only utilized if it will significantly change management. Patients whose RMB reveals benign or indolent histology, may choose AS or a less radical treatment option.[122]

Recently there also has been increased interest in molecular imaging. In particular 99mTc-sestamibi SPECT/CT, has provided another tool to help risk stratify patients. 99mTc-sestamibi SPECT/CT appears to have an 87-93% sensitivity and 95% specificity for identifying benign renal masses (oncocytomas, hybrid oncocytic/chromophobic tumors) from RCC.[123,124] While not yet an established part of guidelines, patients with benign masses on 99mTc-sestamibi SPECT/CT may be better served with AS or NSS.[125]

4. Provider / Surgeon Factors

4.1 *Surgeon Skillset and Technical Experience: RN versus PN, laparoscopic/robotic surgery versus open surgery, transperitoneal versus retroperitoneal approach*

(Potential Influence on Decision Points: 1, 2, 3)

While patient and tumor factors drive decision making choices for treatment of renal masses, surgeon preference and experience cannot be ignored. In fact, this important variable likely contributes significantly to critical decisions regarding whether to proceed with surgery and on which surgical approach to employ.[126-129] As surgical training increasingly incorporates minimally invasive surgical techniques, rates of robot-assisted and laparoscopic RCC surgery have continued to increase internationally with a concurrent decrease rate in utilization of open surgery.[4-6,130] As reported by Paras et al., the diffusion of robotic technology has also enabled increase treatment of SRMs in lieu of AS, and is a cautionary tale that technologic capabilities should not replace our understanding of tumor biology allowing *carte blanche* for surgical intervention.[130] The decision between RN and PN for cT1b-cT2 or complex renal masses, laparoscopic/robotic surgery and open surgery, and transperitoneal vs. retroperitoneal approach for both open and MIS renal surgery is often dependent on the surgeon's training, personal experience and skillset.[69,128,131,132] Ultimately, surgeon comfort with the chosen approach is a prerequisite for acceptable perioperative outcomes.

4.2 Medical center experience & volume (with ablation, PN and advanced renal surgery)

(Potential Influence on Decision Points: 2, 3)

Medical care is increasingly being centralized to centers of excellence, based on the strength of growing evidence that high volume care in centers with established experience yields improved oncologic outcomes.[133-136] The data in RCC similarly support centralization. Indeed, multiple studies have established a volume-outcome relationship for renal surgery, having the strongest impact on peri-operative and short-term oncologic outcomes.[137-140] For example, Hsu et al., in a systematic review and meta-analysis, demonstrated that high-volume centers were associated with a significantly lower mortality for patients undergoing RN [141].

Outcomes of renal mass ablation also appear to be superior at higher volume centers,[7] while uptake of AS has been greatest at academic centers.[142] Utilizing the National Cancer Database, Lawson et al. generated a hospital-level metric of quality "Renal Cancer Quality Score (RC-QS)," which was associated with 30-day, 90-day, and overall mortality. Hospitals classified as 'academic' and those with higher referral volumes were more likely to be higher RC-QS hospitals.[143]

4.3 Health Care System Model – Nationalized/Single-Payer vs. Private

(Potential Influence on Decision Points: 1, 3)

Independent of provider and hospital volumes, the type of health care system in which care is provided likely plays an underappreciated role in approaches to management and outcomes for patients with localized RCC.[126,144] In a private health insurance environment, such as the United States, there are financial incentives to treat patients with surgery or ablation,[145-148] while in countries with single-payer nationalized healthcare, such as the United Kingdom and Canada, there may be an incentive to offer

active surveillance, especially in the context of finite resources and rationing of care delivery.[149-152]

4.4 Access to Multidisciplinary Care (nephrologist, interventional radiologists, oncologists etc.)

(Potential Influence on Decision Points: 1, 2, 3)

As the management of localized RCC now involves multiple specialists, including urologic oncologists, interventional radiologists, medical oncologists and nephrologists, access to multidisciplinary care is critical. From the standpoint of renal function preservation and post-treatment management, early involvement of nephrology colleagues is increasingly important.[78] On the other end of the spectrum, Master et al. highlight the importance of this cross-discipline approach to the management of locally advanced RCC with tumor thrombus, reporting their institution's improvement in perioperative outcomes and 90-day mortality after utilizing a dedicated surgical team.[153] Indeed, multidisciplinary review of patients with RCC may lead to significant changes in treatment plans.[154]

5. Predictive Models & Patient Decision Aids

5.1 Predictive Models/Nomograms

In an effort to better risk stratify patients with localized RCC and help guide physicians and patients towards optimal treatment, multiple established predictive models have been developed and validated to prognosticate disease recurrence.[155-158] Many of these are now routinely utilized in clinical practice and during trial design. Yet, all of these models are based on retrospective data from pre-selected patient cohorts and are thus subject to significant inherent limitations. Indeed, applying these models to a prospectively-collected dataset from the ASSURE trial, Correa et al. demonstrated a sharp decline in the predictive ability of existing models, particularly beyond two years of follow up.[159] The AUC's ranged from 0.55 to 0.68 with 0.5 having the predictive ability of a coin flip. The predictive accuracy of these models was on par with the 2002 TNM staging system (AUC 0.60). Therefore, any future predictive models should be validated in a prospective setting prior to widespread use, while, current models should be used with caution in clinical practice.

5.2 Patient Decision Aids

In contrast to predictive models, which are largely geared to physicians, patient decision aids (PDAs) are underutilized tools to help educate patients prior to shared decision making.[75] Available PDAs for kidney cancer include the International Kidney Cancer Coalition "My Treatment, My Choice",[160] which includes a PDA for patients with small renal masses, and the Canadian OHRI PDA by McAlpine et al.[161] Both are excellent tools for patients considering various treatment options for localized RCC.

Psutka et al. have also reported in abstract form on a similar decision aid for patients that harnessed a multi-institutional cohort to provide cancer-specific mortality, other-cause mortality and 90-day risk of surgical complications for patients undergoing surgery, thermal ablation, and AS.[162]

Limitations

It is important to note that the above factors are not mutually exclusive and the decision-making process is not generally hierarchical. Hence, treatment decision-making for patients with localized solid renal tumors is highly nuanced, often balancing collinear factors that may influence one another. Furthermore, as a collaborative narrative review, the current manuscript does not represent a formal systematic review. Although the authors sought to offer a balanced, evidence-based approach to the question at hand, there is an inherent possibility of bias based on the opinions of the experts involved. Nevertheless, in addition to data from original manuscripts, this work relies on prior systematic reviews and meta-analyses to ensure thorough and comprehensive evaluation of the literature.

CONCLUSION

Treatment decision-making for patients with localized solid renal tumors has become complex and nuanced, reflecting a deeper understanding of the factors influencing discrete goals of treatment. Access to what are multiple effective treatment options, and integration of numerous clinical variables, is mandatory. Development of stronger predictive models and improved adoption of patient decision aids may improve future care delivery in the future.

PATIENT SUMMARY:

With expanding treatment options for localized kidney cancer, treatment decision is highly nuanced and requires shared decision-making. Patient decision aids may be helpful in the treatment discussion.

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FIGURE LEGENDS

Figure 1: Broad View of Localized Renal Mass Treatment Decision Making: Factors Influencing Treatment and Goals of Treatment

Figure 2: Key decision points in the management of newly diagnosed localized solid renal mass

Figure 3: Factors that Influence Decision Point 1 (Active Surveillance vs. Treatment)

Figure 4: Factors that Influence Decision Point 2 (Thermal Ablation vs. Partial Nephrectomy vs. Radical Nephrectomy)

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Take-Home Message

We comprehensively review the influence of patient, kidney, tumor and provider factors on three key decision point in management of localized RCC: (1) decision for surveillance versus treatment, (2) decision regarding treatment modality, and (3) decision on surgical approach.

RESPONSE TO REVIEWERS

We would like to thank the reviewers for their input and constructive comments. We also appreciate the generally positive feedback regarding the writing and organization of the manuscript. We hope we have addressed your comments below. Please find a point-by-point response.

REVIEWER #1

1) The limitations and differences in the evidence acquisition process for this collaborative qualitative review versus a systematic review are important. These should be more clearly delineated upfront.

> Response: To address the point by reviewer #1 and reviewer #4, we have modified the Evidence Acquisition sections in the following ways:
> a) We start the section by stating, "*As established by prior collaborative reviews*, the first and senior authors"
> b) We end the section by stating, "*Ultimately, while not a formal systematic review, we adhered to established journal guidelines for collaborative reviews of this nature.*"
>
> In addition, we have already included in prior revisions a statement in the Limitations section stating "*Furthermore, as a collaborative narrative review, the current manuscript does not represent a formal systematic review. Although the authors sought to offer a balanced, evidence-based approach to the question at hand, there is an inherent possibility of bias based on the opinions of the experts involved.*"
>
> We hope this alleviates the reviewers' concerns as the manuscript clearly establishes up front and reiterates throughout that this is not a formal systematic review. We also highlights that we follow established protocols within the Journal based on precedence of previously published collaborative reviews.

2) Otherwise, while I appreciate that expanding on the section for RTB/histology, further imaging, and future perspectives may be tight within the word count, some of the points mentioned by the Reviewers (as well as those included by the Authors in their responses) would be insightful.

> Response: We appreciate the reviewier's input. We absolutely agree that some of the points mentioned by reviewers and our responses would augment the manuscript; however, we are unfortunately beyond the word count. Expanding these points that are arguably somewhat tangential to the premise of the manuscript, in our opinion, would compromise other salient sections of this work. We have referenced important manuscripts in these respective spaces to which the reader can refer.

REVIEWER #4

1) The authors and the reviewers are familiar with "Collaborative Reviews" in European Urology. However, readers from around the world still may not be, especially if they are only casual readers of European Urology . I stand by my previous suggestions some clarifying statements would be in order.

Response: See Response #1 to Reviewer 1

Figure 1

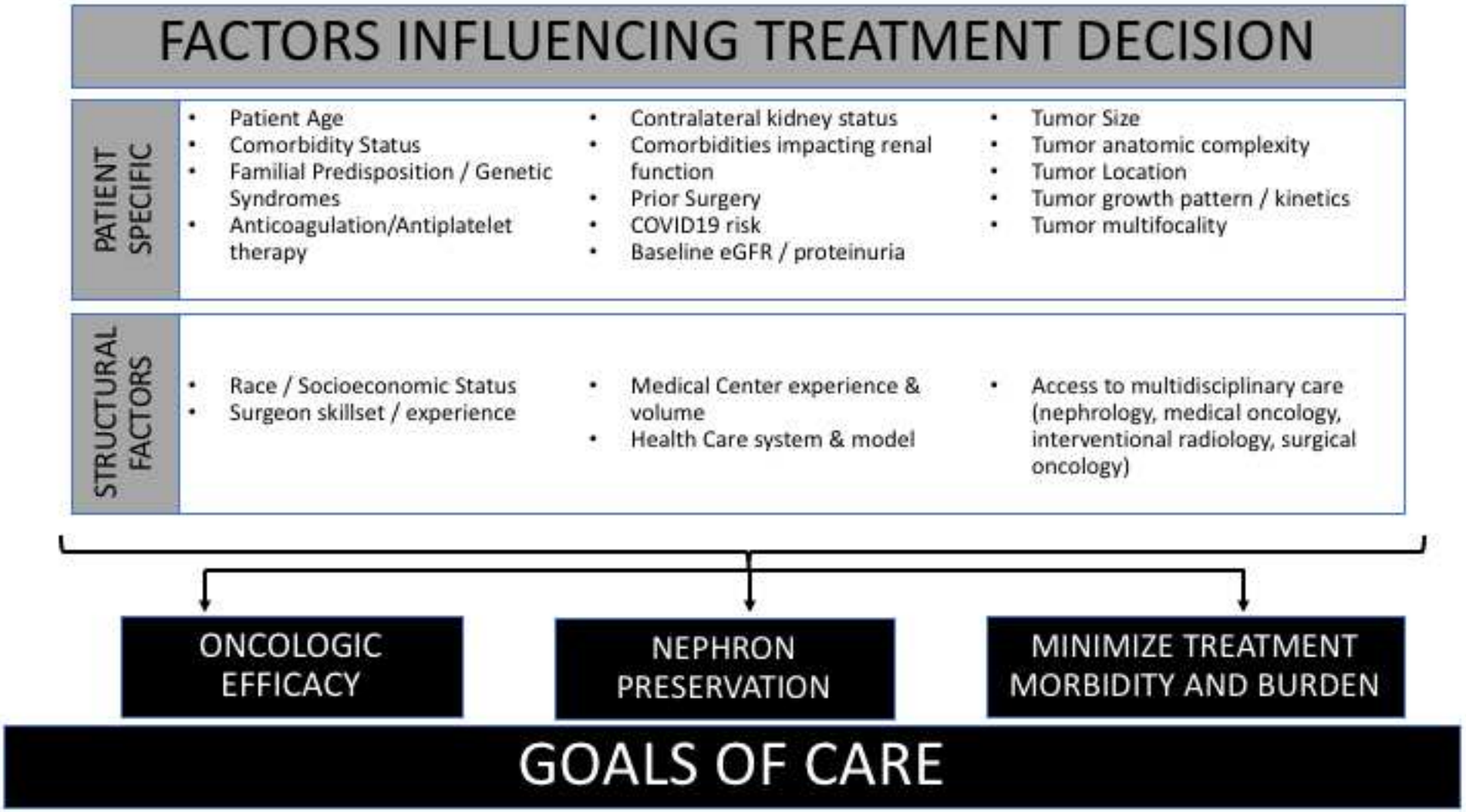

Figure 2

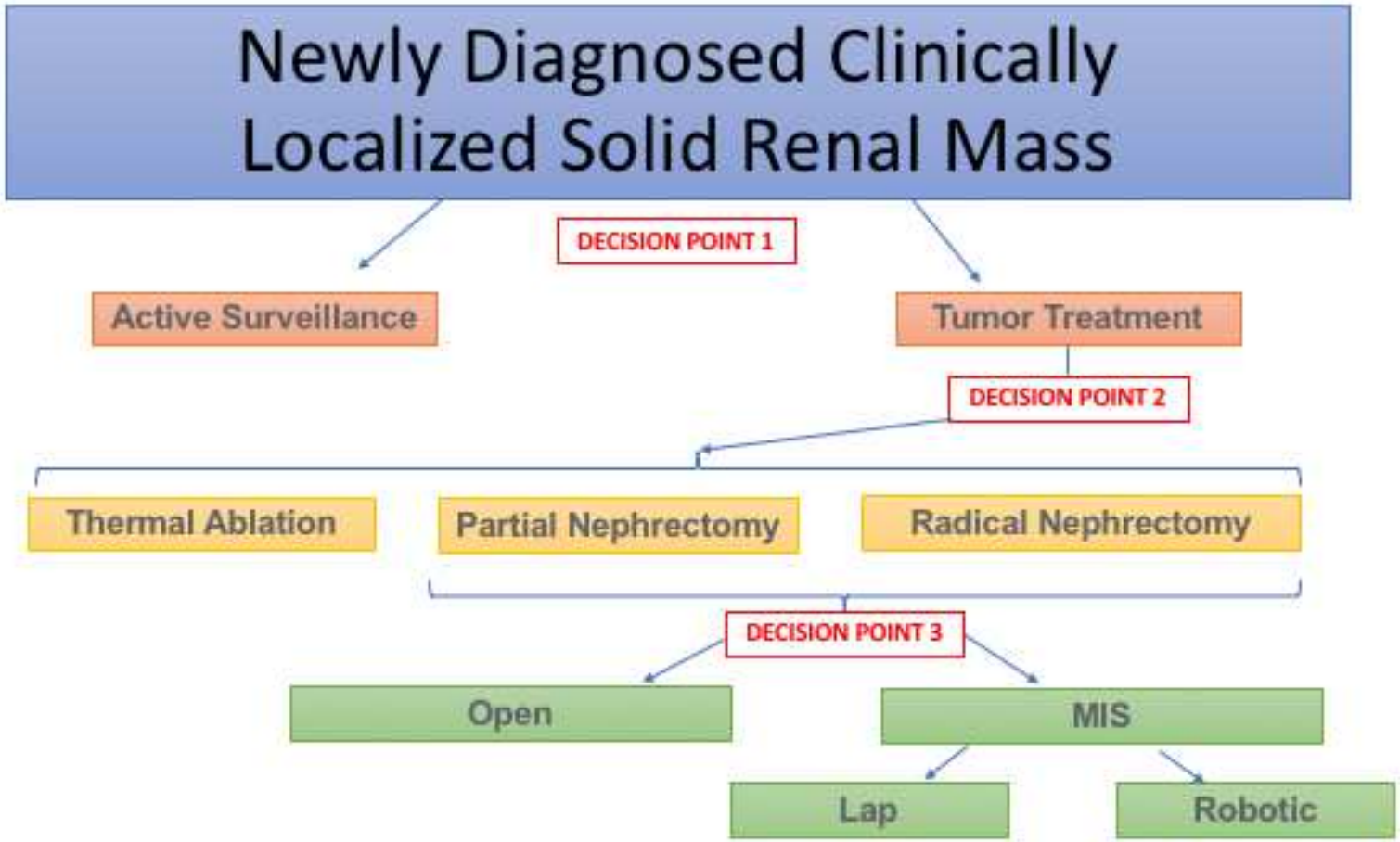

Figure 3

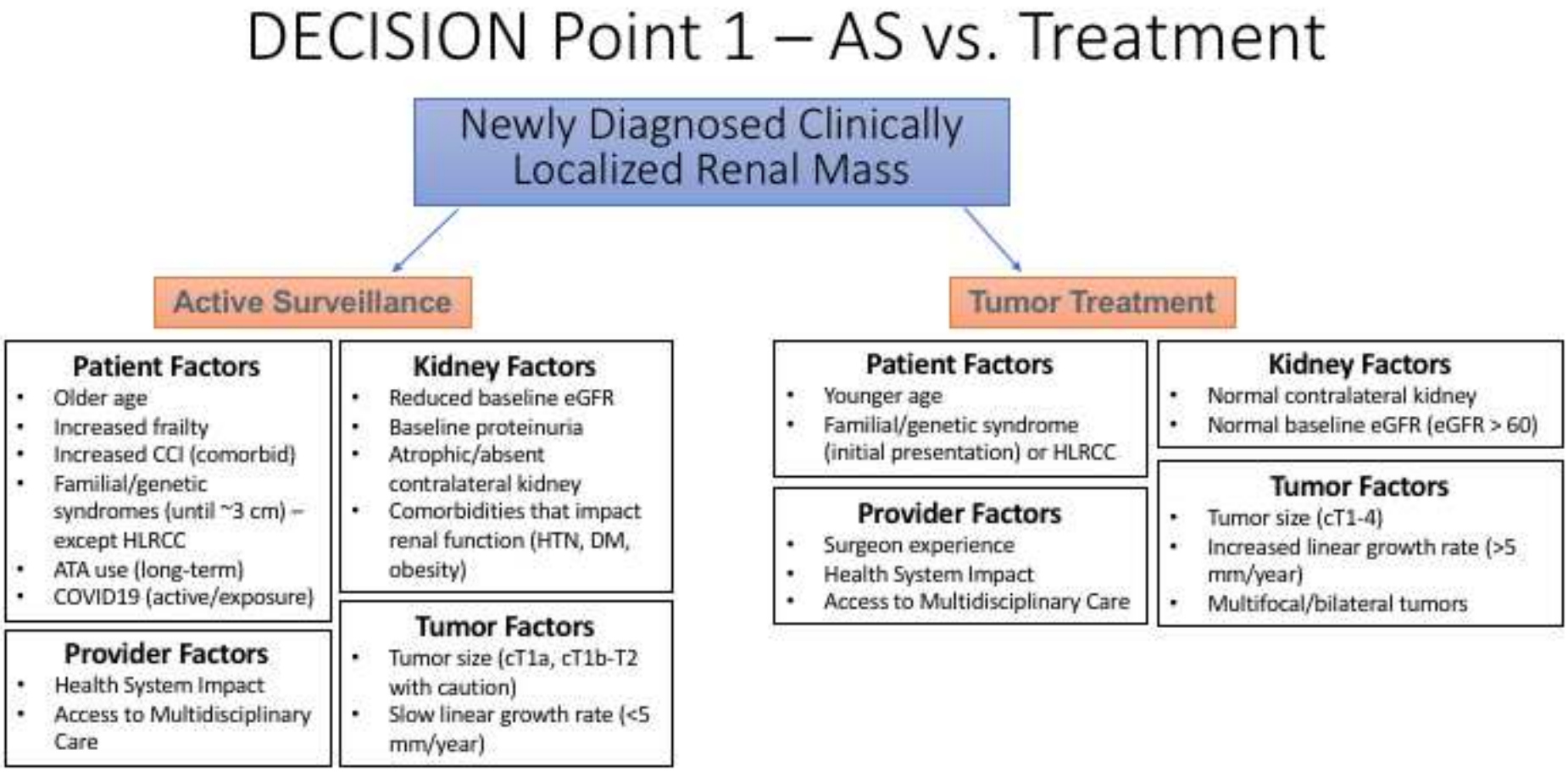

Figure 4