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Platinum Priority – Editorial

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More Isn't Always Better: Time to Derive a Different Strategy for Renal Cell Carcinoma Surveillance

Suzanne B. Merrill *

Division of Urology, Penn State Health Milton S. Hershey Medical Center, Hershey, PA, USA

Oncologic surveillance following treatment of localized disease constitutes a large fraction of renal cell carcinoma (RCC) care despite the lack of level one evidence. This is based on the notion that scheduled follow-up can not only mitigate postoperative complications and patient fear of recurrence but also potentially allow early detection of recurrences. This may then lead to more successful therapeutic options and possibly beneficial patient outcomes. Evidence is increasing that structured RCC surveillance, and detection of asymptomatic recurrences, may afford better prognosis than for patients presenting symptomatically outside of routine follow-up [1,2]. In effort to direct evidence-based care, organizations such as the European Association of Urology (EAU), National Comprehensive Cancer Network (NCCN), American Urological Association (AUA), and Canadian Urological Association have developed surveillance recommendations. However, without high-level evidence validating a preferred frequency, duration, and type of surveillance testing, such guidelines lack consensus and an optimal schedule remains undefined.

Without compelling recommendations on how to effectively navigate such a substantial part of RCC care, oncologic surveillance has become a target for research investigation. In this issue of *European Urology*, Dabestani et al. [3] examine the use of more intensive imaging during follow-up for surgically treated localized RCC as compared to the 2017 EAU surveillance guidelines (Table 1) [4]. Using the RECUR database, a consortium comprising 12 centers from eight European countries, the authors identified 336 RCC recurrences surgically treated from 2006 to 2011 and investigated two objectives: (1) the number of images needed to detect recurrences; and (2) differences in overall survival between patients who had undergone $\leq$0.75 times to $\geq$2 times the amount of imaging recommended by the 2017 EAU guidelines. The authors found that a total of 52 imaging procedures were needed to detect one recurrence, and 697 to identify a high-risk patient currently alive with no evidence of disease following recurrence treatment. Although striking, these numbers may not reflect the authors' intention to communicate a measure similar to "number to treat." In order to derive the effectiveness of an intervention (imaging) for an outcome, event rates for both patients who develop recurrence and those who do not need to be determined. From these rates an absolute risk reduction can be calculated and transformed into a meaningful "number of images needed to detect" statement. In this study, the authors derive this statement by dividing the number of recurrences by the total images performed on all RCC patients of a particular risk group. Unfortunately, this methodology fails to translate into a meaningful epidemiological measure.

For the second study objective, the authors found no significant differences in overall survival when either less or more intensive surveillance imaging was used in comparison to the 2017 EAU guidelines. Interestingly, to perform this comparison of the actual versus recommended amount of imaging, the recurrence cohort required truncation by 12% (n = 43). As the EAU provides no recommendations for imaging before 6 mo or after 5 yr for low-risk patients, recurrences detected in these time periods were eliminated as no comparative analysis could be made. In addition, the authors found that the surveillance imaging utilized consisted of conventional modalities (chest X-ray/ultrasound) among 53% of patients. The 2017 EAU guidelines state a preference for cross-sectional imaging but allow

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* Division of Urology, Penn State Health Milton S. Hershey Medical Center, 500 University Drive, P.O. Box 850, Hershey, PA 17033, USA.
Tel. +1 717 5318848; Fax: +1 717 5314475.

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Table 1 – European Association of Urology 2017 renal cell carcinoma surveillance guidelines

Risk profile [a]	Surveillance						
	6 mo	1 yr	2 yr	3 yr	4 yr	5 yr	> 5yr
Low	US	CT	US	CT	US	CT	Discharge
Intermediate	CT	CT	CT	US	CT	CT	CT once every 2 yr
High	CT	CT	CT	CT	CT	CT	CT once every 2 yr

CT = computed tomography of the chest and abdomen (alternatively, use magnetic resonance imaging); US = ultrasound of the abdomen, kidneys, and renal bed.
[a] Risk according to the University of California Los Angeles integrated staging system.

conventional modalities every other visit for low-risk patients and only once for intermediate-risk patients (Table 1). A preference for cross-sectional imaging is stipulated as it allows recurrences to be detected at smaller volumes [4]. Detection of recurrences when the tumor burden is lower may afford more effective therapeutic options, and recurrence size has been positively correlated with increasing disease-specific death [5].

Evaluation of the impact of surveillance strategies on patient outcomes is challenging. Retrospective analyses are subject to inherent variation in surveillance schedules and imaging. Analysis of the effects of surveillance is complicated by differences in treatment efficacy and variances in disease biology. Only surveillance regimens in breast [6] and colorectal cancer [7] have been evaluated in a randomized setting. More intensive surveillance did not improve disease-specific survival in either cancer. Although no such trial has been performed in RCC, Dabestani et al. [3] should be commended for this work on surveillance. It adds evidence to the existing literature indicating that simple modifications to current guidelines appear to be ineffective.

In 2014 we evaluated the NCCN and AUA RCC surveillance guidelines and found that if strictly followed, up to one-third of all primary recurrences could be missed. To capture 95% of recurrences, existing protocols would need to extend their follow-up duration beyond 10 yr for all risk groups [8]. With cancer costs estimated to exceed $173 billion in the USA by 2020 and surveillance being a target for future cost cuts [9], simple extension of the existing guidelines is unreasonable. Thus, in an effort to develop a more effective strategy, we began to restructure the backbone of current guidelines: estimation of RCC recurrence risk. At present, the majority of the guidelines use only disease-related variables and assume that the recurrence risk remains static. However, this strategy poorly reflects how a patient's recurrence risk decreases with longer survivorship and is influenced by competing comorbidities. From this perspective, we developed a protocol founded on a competing-risk strategy to establish reasonable stopping points for surveillance when a patient's risk of non-cancer death, stratified by age and comorbidity status, exceeds their risk of RCC recurrence stratified by stage and relapse site (Table 2) [10]. This method appeared to better contextualize a patient's natural RCC course and allow identification of when a patient's competing health conditions may drive survival to a greater extent than their cancer. Although this novel approach addresses some of the limitations of current guidelines, its performance has not

Table 2 – Time points in years specific to age, CCI, stage, and relapse location at which the risk of non-RCC death exceeds the risk of recurrence of RCC [a]

Stage group and relapse location	Time point (yr)									
	Age <50 yr		Age 50–59 yr		Age 60–69 yr		Age 70–79 yr		Age ≥80 yr	
	CCI ≤1	CCI ≥2	CCI ≤1	CCI ≥2	CCI ≤1	CCI ≥2	CCI ≤1	CCI ≥2	CCI ≤1	CCI ≥2
pT1 Nx–0										
Abdomen	>20	–	7	–	2.5	–	1.5	–	0.5	–
Chest	>20	–	1	–	1	–	0.5	–	–	–
Bone	0.5	–	0.5	–	0.5	–	0.5	–	0.5	–
Other	–	–	–	–	–	–	–	–	–	–
pT2 Nx–0										
Abdomen	>20	0.5	10.5	0.5	5	0.5	2.5	0.5	1	–
Chest	>20	0.5	14	1	6	1	3	0.5	1.5	–
Bone	>20	–	6.5	–	3	–	1.5	–	1	–
Other	>20	–	2.5	–	2	–	0.5	–	0.5	–
pT3/4 Nx–0										
Abdomen	>20	5	19.5	3	9	2.5	5	1.5	2	0.5
Chest	>20	14	>20	5.5	12.5	4.5	6	1.5	2.5	1
Bone	>20	0.5	7.5	0.5	4	0.5	2.5	0.5	1.5	–
Other	>20	0.5	10	0.5	5.5	0.5	2	0.5	1	–
pTany N1										
Abdomen	>20	>20	>20	>20	>20	>20	13	8	5	3
Chest	>20	>20	>20	>20	>20	14	10.5	5.5	4.5	2
Bone	>20	4.5	20	3	9	2.5	4.5	1	2	0.5
Other	>20	>20	>20	10.5	13	4.5	6.5	2	2.5	1

RCC = renal cell carcinoma; CCI = Charlson comorbidity index;– = risk of non-RCC death exceeds the risk of RCC recurrence starting at 30 d after surgical resection, suggesting surveillance may not be necessary.
[a] From Stewart-Merrill SB et al, J Clin Oncol 2015;33:4151–7 [10], with permission.

been rigorously evaluated. However, it sets an example of how guidelines can be transformed into more sophisticated strategies.

In summary, the study by Dabestani et al. [3] reveals that more surveillance is not always better. An individualized strategy that allows plasticity and is not completely RCC-centric may be more effective. Guideline optimization is becoming more pervasive as oncologic surveillance is targeted for cost cuts. Our ability to effectively restructure RCC guidelines will be predicated on balancing medical necessity with economic sustainability.

Conflicts of interest: The author has nothing to disclose.

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