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Postoperative surveillance imaging for patients undergoing nephrectomy for renal cell carcinoma

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Abstract

The American Urological Association and the National Comprehensive Cancer Network guidelines regarding postoperative surveillance for renal cell carcinoma (RCC) have provided a standardized framework for imaging following nephrectomy. These stage-stratified recommendations are based on retrospective studies that identified the timeline and location of RCC recurrences. However, the simplified and generalizable protocols offered by the American Urological Association and the National Comprehensive Cancer Network are not without limitations. Studies have found that RCC recurrences continue to be missed even with perfect compliance to these protocols and that RCC recurrences occur not infrequently after the required surveillance window of 5 years. Furthermore, recent studies evaluating the use of adjuvant systemic therapy in patients who are at a high risk for RCC recurrence or metastasis after nephrectomy have yielded disappointing results. This calls into question what interventions we can offer patients to improve survival once RCC recurrences are detected during postoperative surveillance; an effective surveillance strategy requires effective treatment options. The future of personalized medicine with genetic profiling of patients with RCC may offer a potential solution by providing better risk stratification to determine the intensity of surveillance imaging as well as to determine which patients will actually derive survival benefit from intervention on recurrent disease.

Keywords

Renal cell carcinoma; Surveillance; Recurrence; Diagnostic imaging

Numerous studies have used retrospective observational data of renal cell carcinoma (RCC) recurrences after nephrectomy to generate surveillance imaging protocols following partial and radical nephrectomy for localized RCC [1–4]. The basic tenets of these protocols include risk-stratified imaging intensity, with less surveillance for those with low-risk disease, and decreased imaging frequency with increasing time from surgery. Risk groups are based on tumor stage, pathologic features, and the Eastern Cooperative Oncology Group performance status. There are 2 studies that recommend discrete total duration of surveillance imaging (9 and 10 y in the studies by Lam et al. and Siddiqui et al., respectively), and 2 other studies recommend indefinite continuation of surveillance imaging.

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The recent guidelines regarding postoperative surveillance for localized RCC published by the American Urological Association (AUA) and the National Comprehensive Cancer Network (NCCN) are notably shorter in duration than the protocols cited earlier [5,6]. For low-risk patients (defined as having T1 category disease by both the organizations), recommendations include (1) yearly chest x-ray for 3 years, (2) baseline abdominal imaging within 3 to 12 months following surgery, and (3) optional yearly abdominal imaging for 3 years if the patient underwent partial nephrectomy. For moderate- to high-risk patients (having T2–T4 category disease or any N1 category for the AUA and T2–T3 category disease or any N1 category for the NCCN), recommendations include (1) baseline chest and abdominal imaging within 3 to 6 months following surgery and (2) continued chest and abdominal imaging every 6 months for 3 years, and yearly thereafter to 5 years.

Although the AUA and the NCCN guidelines form the most practical framework for postoperative RCC surveillance, their ability to successfully capture RCC recurrences has been criticized. In a retrospective study of 3,651 patients who underwent partial or radical nephrectomy for localized RCC, of whom 30% developed disease recurrence, Stewart et al. [7] found that strict adherence to the NCCN and the AUA guidelines would still have missed approximately 33% of recurrences, with abdominal recurrences in low-risk patients being the greatest proportion of missed recurrences. In another retrospective study of 1,454 patients who were disease free for at least 5 years after nephrectomy, Kim et al. [8] found that 4% and 12% of patients eventually developed local and distant disease recurrences, respectively. These studies suggest that the current standards for RCC surveillance are inadequate; stage alone does not provide an accurate assessment of recurrence risk, and the duration of continued surveillance of imaging appears to be arbitrary.

Especially when considering the cost of health care, as well as the risks associated with cumulative radiation exposure [9], increasing the imaging frequency and duration for all patients to detect a higher proportion of RCC recurrences is not a reasonable solution. Using the current AUA and NCCN guidelines, Stewart et al. estimated postoperative RCC surveillance costs between $1,740 and $3,700, whereas the cost of surveillance imaging to detect 95% of recurrences is estimated between $9,860 and $13,090 [7]. This is not an insignificant sum when considering the cost of surgery to be between $13,300 and $27,900 [10] and the lifetime estimated costs associated with diagnosis of RCC to be between $33,010 and $51,360 [11]. Instead, tailored postoperative surveillance protocols based on improved risk stratification are needed to reduce unnecessary scans, and therefore cost, while simultaneously improving detection of recurrences. Studies have considered clinical and pathologic variables beyond tumor stage alone that are linked to disease progression and late RCC recurrence (beyond 5 y), including symptomatic presentation, sarcomatoid pathology, tumor necrosis, nuclear grade, and lymphovascular invasion [2–4,12–14]. However, creating surveillance strategies based on better-detailed clinical and pathologic algorithms is much more difficult to apply to practice, and they are unlikely to be used unless clear improvements in survival can be linked to such a strategy.

Demonstrating an improvement in survival after nephrectomy for RCC based on different surveillance imaging regimens is very difficult. Previous retrospective studies contain bias owing to patient selection and lack of an observation (or comparator) arm. A randomized,

prospective comparison of surveillance regimens would eliminate these biases; however, earlier detection of recurrences (associated with longer duration and higher frequency of imaging) always increases apparent survival from the time of disease recurrence owing to lead time bias. More importantly, surveillance imaging does not affect survival without effective interventions for the image-detected recurrences. Although retrospective studies have demonstrated positive outcomes after early detection of isolated nodal, local, and pulmonary recurrences that were treated surgically [15–17], these cases may represent patients with biologically less-aggressive disease, as those with late recurrences have also been found to respond better to adjuvant treatment and have improved overall survival compared with that of those with early recurrences [18]. Owing to these challenges in demonstrating a clear connection between survival and surveillance imaging, a prospective trial comparing the benefit of various surveillance regimens may need to rely on end points other than on survival (e.g., patient satisfaction and quality of life).

To determine an effective postoperative surveillance imaging protocol, we must have effective and available interventions for those with image-detected RCC recurrences. A first step in determining if best available systemic therapy can improve survival for patients who develop RCC recurrences may be up-front treatment with the same therapies for patients with high-risk disease after nephrectomy. Unfortunately, 2 prospective randomized studies comparing adjuvant treatment for patients with high-risk disease after nephrectomy have yielded disappointing results. Aitchison et al. randomized 309 patients with localized but high-risk features (having T3b or higher category disease, positive nodal disease, positive surgical margin, and vascular invasion on pathology) to adjuvant 5-flurouracil, α-interferon, and interleukin-2 or observation beginning at 8 weeks after nephrectomy. At 7-year median follow-up, they found no significant differences in 5-year survival between the groups, with significant toxicity in the treatment arm [19]. Despite advances in treatment with targeted therapy, early results from the Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma (ASSURE) trial are equally disappointing. At interim analysis, no differences in survival have been noted for patients in the sorafenib, sunitinib, and placebo arms [20].

Up-front adjuvant therapy for patients with high-risk disease may not have been found to be beneficial, because the current tools for patient risk stratification may be inadequate at determining who is most likely to develop disease recurrence and also inadequate at determining who will benefit most from systemic therapy. One solution may lie in personalized medicine, where genetic tests are performed on both the patient and their surgically resected tumor to help predict the likelihood of developing recurrent disease (to tailor postoperative imaging surveillance) and the likelihood of a response to a particular targeted therapy (to tailor adjuvant or salvage systemic treatment) [21].

Recent studies have examined genetic profiling of RCC, the association between these genetic profiles and patient outcomes (recurrence and survival), and the differences in response to available systemic therapies based on their profile. Although a paradigm shift in postoperative RCC surveillance from standardized protocols to personalized medicine requires more well-designed prospective studies, early evidence suggests that this may be the future of the field. Both a 16-gene assay and a 34-gene assay of clear cell RCC specimens have demonstrated significant associations with the likelihood of disease

recurrence [22,23]. Haddad et al. [24] describe validation of a 5 mammalian target of rapamycin (mTOR) pathway gene panel and oncologic outcomes in 528 patients. Although they did not study the treatment response of patients with recurrent disease based on their mTOR pathway profile, the link between their study findings and selective use of mTOR inhibitors appears to be the next translational step. Choudhury et al. report on this translational step by identifying an 8-gene panel to generate prognostic subtypes of clear cell RCC from tumor tissue. The correlation of their 8-gene panel with cancer-specific survival was validated in 3 separate cohorts, and for a small subset of patients receiving tyrosine-kinase inhibitors, their gene panel was significantly associated with radiologic response to treatment and survival while on tyrosine-kinase inhibitor therapy [25].

Although seemingly promising, genetic testing and personalized medicine in the management of RCC raise important questions. Firstly, it is not clear whether this personalized approach increases or reduces total costs to the health care system. Although one may postulate that personalized surveillance and treatment would reduce the total amount of postoperative imaging obtained, specifically by reducing imaging for patients with minimal risk of recurrence and for patients without available interventions known to improve survival, the costs of widespread genetic testing of all patients and their tumors would likely outweigh these savings. Secondly, determination of the genetic profile of RCC does not necessarily provide that gene-based drug targeting is possible or that these drugs would be developed. A recent example includes the identification of BRCA1/2 for breast cancer and ovarian cancer, as these patients are offered increased and early screening and preemptive surgery, but no targeted therapy for this particular mutation has been developed to date. Finally, personalized genetic testing as well as mutation-specific targeted therapy would likely present an enormous cost to the particular patient, using current RCC-specific targeted therapy as a frame of reference (sorafenib $10,555 per month, sunitinib $11,957 per month, everolimus $8,984 per month, temsirolimus $6,355 per month, pazopanib $7,778 per month, and bevacizumab $11,684 per month) [26].

The issue of postoperative surveillance imaging for patients with RCC undergoing nephrectomy with curative intent cannot be divorced from the issue of treatment for recurrence of RCC in these patients. Although the AUA and the NCCN guidelines provide a basic framework for surveillance, there are oncologic limitations to such a simplified, cost-effective, and generalizable approach. Additionally, the survival effect we are capable of making by intervening on those with detected RCC recurrences at this time is at best unclear. A personalized approach to oncologic care for RCC that relies on genetic profiling may provide the necessary stratification tool to tailor postoperative surveillance imaging for those with higher risk for recurrent or metastatic disease as well as those who will benefit from intervention with specific systemic treatments.

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