Editorial Commentary

Post-operative surveillance in kidney cancer

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Currently, there is no single accepted protocol for post-operative surveillance programs after an allegedly curative surgery for renal cell carcinoma (RCC). Guidelines often suggest a stage-based imaging protocol. For instance, the European Urological Association guidelines recommend for low-risk patients abdominal ultrasonography at 6 months postoperatively, then CT of the chest and abdomen after 1, 2 and 3 years and then every two years. For high-risk patients, CT of the chest and abdomen 6 months postoperatively and then after 1, 2, 3 years and then every two years (1).

To be useful for the patient, a surveillance program must fulfil many requirements:

(I) The imaging modality should be sensitive for the diagnosis of tumor recurrence.
(II) The imaging modality should be sensitive for diagnosis of post-operative complications.
(III) The imaging modality should not expose the patient to a significant danger since many healthy people will be exposed to it.
(IV) The imaging modality should be available and not too expensive.
(V) Early diagnosis of recurrence (by the surveillance program) should provide prognosis benefit compared to late diagnosis (by symptoms).

Unfortunately, thus far, the surveillance protocol suggested by the EAU above did not fulfil the last requirement, i.e., it did not provide survival benefit (2). Better programs are certainly needed.

What do we know about the utility of PET/CT in the diagnosis of RCC recurrence? Most studies asking this questions were done with FDG as radiotracer (3). It is acceptable that PET/FDG has a higher overall success rate in detecting metastases compared to CT. Aide *et al.* studied 53 patients with various primary tumors and observed that FDG detected all metastases demonstrated by CT and 8 additional sites, leading to an accuracy of 94%, compared to 89% for CT (4). Although not routinely used for diagnosis of metastases, PET/CT can be used in cases of ambiguous findings on CT to support or refute the diagnosis of metastases (5).

The recently published manuscript "Clinical utility of 68Ga-DOTATOC positron emission tomography/computed tomography for recurrent renal cell carcinoma" by Nakamoto *et al.* is a retrospective analysis of 25 patients that had surgery for kidney, cancer 1–350 months before the PET/CT (6). All patients had "known or suspected recurrent RCC". The authors found 76 "confirmed lesions". The commonest sites of these lesions were the bones (32 lesions), the lungs (15 lesions) and the pancreas (6 lesions). From this information, the authors concluded "that DOTATOC-PET/CT would be useful for detecting recurrent foci in patients with clear cell RCC".

Unfortunately, at least to our mind, the data provided in the manuscript does not support the conclusion. Firstly, the authors do not provide information on how the patients were selected. It is said that they had "known or suspected recurrent RCC" but it is not written how this knowledge

was gained. Was another "gold standard" imaging modality used before the PET to provide this knowledge? Secondly, the timing of scanning was 0–30 years after surgery. This huge span of time is very far from what is considered a routine post-operative surveillance. The median time for recurrence of RCC is 16 months (7). Thirdly, the authors state that they found 76 "confirmed lesion", but table 1 shows that histological confirmation was available only in half of the cases. So it is not clear how did the lesions became "confirmed". Fourthly, a close look at the list of recurrence sites suggests that many of them could have been false positives. The commonest sites of metastases in that study were the bones (42%), the lungs (19.7%) and the pancreas (7.8%). The order of involved organs in this series is different from the accepted order in the literature. For example, in a study of 493 patients followed by periodic CT scanning of the chest and abdomen, recurrence developed in 83 patients (16.6%). The commonest sites for recurrence were the lungs (64.6%), the bones (10.9%) and the adrenals (6.1%). Recurrences in the pancreas were not observed (8). It should be mentioned that uptake of DOTATOC in the pancreatic head and especially in uncinated process is well known part of normal biodistribution of this tracer and can be confused with pathological uptake. However, the issue of pancreatic recurrence is interesting and will be addressed later.

So what does the study of Nakamoto *et al.* (6) adds to our knowledge? It suggests that at least some of the RCC recurrences demonstrate DOTATOC uptake and therefore exhibit neuroendocrine features. This could be an underreported and not an uncommon phenomenon. Nadebaum *et al.* reported on 3 patients with pancreatic tumors and history of RCC. DOTATATE uptake in the pancreas led to the clinical diagnosis of neuroendocrine tumor but histology showed RCC metastases (9). The reason for this phenomenon is the amplification of the somatostatin receptor 2 transcript (10,11). Neuroendocrine activity was reported also in other types of malignancy like prostate cancer (12). This phenomenon can have diagnostic and therapeutic implications.

PET/CT as any other imaging modality should not be routinely used for surveillance after treatment of RCC until a different research modality is employed. So how does a research that can potentially provide a useful test for detecting recurrent RCC should look like?

(I) The study should be based on through knowledge of the biology of RCC including its recurrence locations and timing according to the stage, grade, histological sub-type and other parameters of the disease. For instance, there is no reason to survey the thighs as was done in the study of Nakamoto *et al.* since there are no recurrences there. Furthermore, surveying the lower abdomen may also be unnecessary since the risk of recurrence developing there is also very low (8).

(II) The study should be based on knowledge of the potential risks of the imaging study itself. The danger of repeated exposure to X-ray is not negligible even in older patients. Specifically, CT scanning is associated with significant exposure to ionizing radiation (13). The biological effect of radiation is expressed in Siverts (Sv). The average dose of a single CT of the chest, abdomen, and pelvis is 21 mSv which is equal to 7 years of exposure to the natural background radiation or to standing 2 km from the atomic explosion in Hiroshima. According to the "linear no threshold theory", a single CT of the chest and abdomen adds a cancer risk of 1 in 942 to a 50-year-old male and 1 in 704 to a 50-year-old female (14).

(III) The study should be prospective and should recruit most and preferably all operated patients in several institutions. Patients should be randomized into two arms; the control arm should receive the standard, state of the art, follow-up (1) and the study arm that receives the experimental follow-up protocol.

(IV) The most significant (and probably the only significant) parameter in evaluation of the study results should be overall survival. An effective surveillance protocol should extend the overall survival of the patients. Any other parameter including disease-specific survival, metastases-free survival etc., is subject to confounders.

PET/CT or any other imaging modality should not be used for routine surveillance after treatment of RCC until this type of methodology is employed in a prospective study and a proof that the imaging modality prolongs overall survival is shown. This does not mean that PET/CT has no place today in the post-operative evaluation of RCC patients. Its main place is in the evaluation of marginal cases such as new small pulmonary or retroperitoneal lesions in a post-operative CT of patients after surgery for RCC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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