Handling, sampling and stage evaluation of renal cell carcinoma: a practical guide

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Abstract

Tumor stage is considered the single most important prognostic factor in renal cell carcinoma. The most critical issue when determining the pathologic stage is whether the tumor is organ-confined or has spread outside of the organ and invaded the perinephric tissues and the adjacent structures. Proper handling and sampling of nephrectomy specimens is essential for accurate determination of pathologic stage and other relevant tumor parameters. Tumor staging requires careful assessment of various tumor characteristics, including tumor size, extent of tumor invasion in relation to specific kidney structures (sinus fat, renal vein and its segmental branches) and perinephric tissues (perinephric fat, Gerota fascia, adrenal gland and vena cava). Therefore, it is imperative that pathologists are familiar with the normal renal anatomy and histology, able to properly dissect surgically resected renal tumors, and able to assess specimens grossly and microscopically, to accurately determine and report pathologic stage and other relevant tumor parameters.

Keywords fat invasion; International Society of Urological Pathology; ISUP; kidney; renal cell carcinoma; renal sinus; renal vein invasion; specimen handling; stage

Introduction

Tumor stage is the single most important prognostic factor in renal cell carcinoma (RCC).[1,2] Tumor stage has also been incorporated into several outcome predictive models and nomograms for RCC used in clinical practice for prediction of survival, metastatic disease, and recurrence.[3] The current TNM staging system (2010 edition, 7th edition) for RCC has been validated as a powerful prognosticator for RCC.[4–6] Although several experts and expert groups have published recommendations on handling and dissection strategies for evaluation of RCC (see details in Trpkov et al[7]), until recently there was no universally accepted handling and sampling approach. To address these issues the International Society of Urologic Pathology (ISUP) formed an expert working group to focus on the RCC staging and specimen sampling. This work was part of the ISUP Renal Cancer Consensus Conference, which was held in Vancouver in March 2012. The ISUP working group electronically polled the ISUP members prior to the meeting and at the meeting regarding many issues important for specimen handling and staging, and led the meeting discussion with a focus on establishing a consensus (≥65% agreement among participants) regarding the key questions. The resulting paper on this topic represented the consensus recommendations and practical guidelines for handling and staging of RCC,[7] and the review presented herein follows the framework outlined in that paper. We have additionally included suggestions and practice recommendations based on our own experience from a busy genitourinary pathology practice.

The objective of this review is to focus on practical aspects of nephrectomy specimen handling, sampling and gross and microscopic evaluation in reference to relevant kidney anatomy and RCC staging parameters, and to provide guidance to pathologists and pathology laboratory technicians for optimal sampling and accurate staging of RCC.

Initial handling and inking of nephrectomy specimens

The proper orientation is the first step in the handling of renal specimens, which allows identifying the key external landmarks. The knowledge of kidney laterality aids in locating the adrenal gland, vascular resection margins and the ureteral stump, all of which are located on the inner (medial) aspect of the specimen. Adrenal gland is typically located within the fat at the upper pole of the kidney but may not be present depending on the specimen type. The hilar, mid-specimen region contains the clamped renal artery and vein resection margins. Ureteral stump may vary in length, and if longer, typically extends towards the lower pole of the kidney. Opening and examining the mucosal surface of the ureteral stump for any abnormality and sampling its margin should be one of the routine steps during the initial specimen examination. The margins of hollow structures in a radical nephrectomy including renal vein, renal artery and the ureter, are sampled routinely en face.

The inking of partial and radical nephrectomies is also routinely used to assess the resection margins, and to visualize and establish the relationship of the tumor with the perirenal fat and the Gerota's fascia. The ISUP consensus advocated using ink both for partial and radical nephrectomies.[7] However, in partial nephrectomies, ink is applied primarily to assess the parenchymal resection margin (Figure 1A). Inking the complete surface of partial nephrectomies is also practiced by some, but not the majority of genitourinary pathologists. Applying ink on radical nephrectomies is also a common practice, which is however somewhat variable. Focal inking applied only on suspicious areas (Figure 1B) is our preferred method, while some pathologists ink the whole specimen surface. Both methods are acceptable in practice. Painting the whole surface of the specimen is more time consuming, but may be preferred in laboratories that infrequently deal with nephrectomy specimens. This

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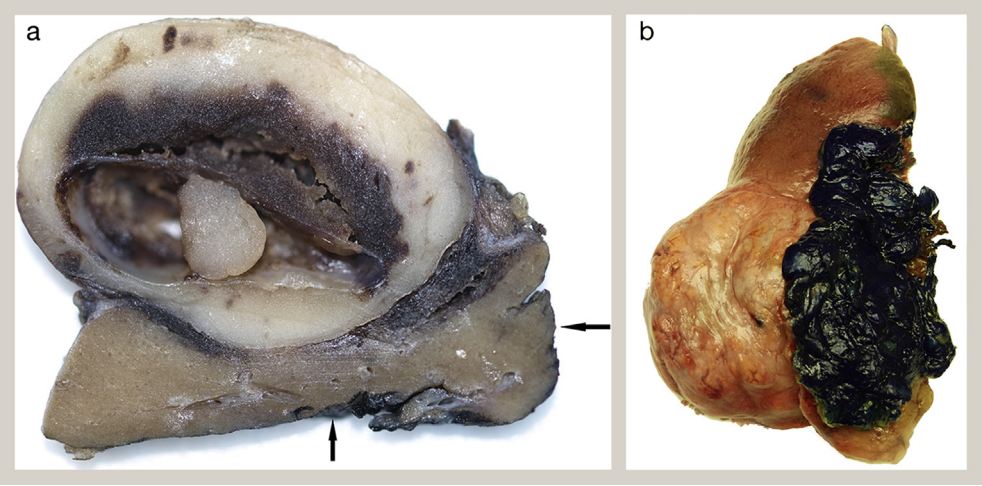

Figure 1 (**a**) A partial nephrectomy specimen with inked parenchymal resection margin (arrows). (**b**) A radical nephrectomy specimen with partial inking over the underlying tumor. Perirenal adipose tissue has been carefully stripped from the non-neoplastic kidney surface and part of tumor surface where it could be removed, and is retained over an area of possible perirenal fat invasion.

approach may also aid in separating the perinephric fat from the sinus fat on microscopic examination.

Inking may not be necessary in many routine specimens. The primary objective is to facilitate accurate margin assessment, particularly in partial nephrectomies. However, the evidence for mandatory inking specimen margins is not compelling as a positive margin does not appear to predict recurrence in partial nephrectomies.[8]

Initial dissection of nephrectomy specimens

Radical and partial nephrectomies are typically processed after fixation, therefore they first need to be opened to allow adequate fixation. Radical nephrectomy specimens are typically opened along the long axis of the kidney either from the lateral or the medial aspect, which was supported by the ISUP consensus.[7] To guide the specimen bivalving and to ensure good visualization, we prefer to insert probes into the largest hilar veins. The main renal veins are located anterior to the renal pelvis. Opening the specimen through the hilar veins enables visualization of possible main renal vein invasion. An alternative method is to bivalve the specimen through the collecting system, which allows cross-sectional view of the collecting system and better exposure of the tumor–renal sinus interface. In some cases, additional cuts may be necessary to better expose the tumor and demonstrate its relationship with the adjacent structures. This is in particular true for larger tumors. Partial nephrectomy specimens are typically sectioned perpendicular to the surgical parenchymal margin, which allows for optimal margin assessment (Figure 1A).

Measurement of tumor size

The greatest tumor dimension is considered one of the key determinants of tumor stage and has been shown to have prognostic significance. Multiple cuts through the tumor may often be required (either parallel or perpendicular) to establish the greatest tumor dimension. We routinely measure tumor size in three dimensions. The ISUP consensus established that the tumor measurement should include the tumor extending beyond the kidney into the peripheral extracapsular tissue and the renal sinus, but should not include any tumoral component (or tumor thrombus) extending into the main renal vein or vena cava (Figure 2A–B). In particular, the relevant cutoff points (4, 7, and 10 cm) are important for accurate staging. The 7 cm is probably the most important cutoff point, as tumors greater than 7 cm have sinus fat invasion in greater than 90% of cases (stage pT3a or worse).[9]

Although the 7th edition of the TNM staging maintained the division of stage pT2 into T2a (organ-confined 7–10 cm) and T2b (organ-confined >10 cm), this division does not appear to be predictive.[10] In addition, pT2 stage should be quite rare in practice, as many pT2 tumors represent under-sampled pT3a tumors that have unappreciated sinus fat, perirenal fat or vein invasion.

For specimens with multiple tumors, the largest diameter of each tumor should be recorded for up to a maximum of five tumors. Recording the sizes of the largest two tumors and providing a size range for the remaining ones is an acceptable and reasonable approach. The largest tumor should be used for pT staging. An exception is when the smaller tumor(s) demonstrate higher stage with perirenal fat, renal sinus or renal vein invasion. We recommend that the information about the different stages of the index and smaller tumors is clearly communicated in the report in this rare scenario.

Tumor sampling

The number of tissue blocks that should be sampled from the tumor depends primarily on its size and gross heterogeneity. The optimal sampling strategy should allow for accurate assessment of histologic type, stage, grade, surgical margin(s), necrosis and other relevant prognostic findings, such as sarcomatoid or rhabdoid areas. The consensus guideline calls for one block per cm of the tumor, with a minimum of three blocks (subject to modification as needed in individual cases).[7] Tumor

