Natural History of Renal Cell Carcinoma

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Introduction

With the increasing use of imaging modalities such as ultrasonography and computed tomography as screening modalities, renal cell carcinoma (RCC) can now frequently be detected asymptptomatically in the early stages. As a consequence, the rate of incidental detection has increased from 10% to greater than 60% over the past 30 years (11, 16), thus resulting in a significant downward stage migration (18). In the era when such modalities were not available, RCC tended to be diagnosed based on the local symptoms of the patients including hematuria, flank pain, and a palpable mass. Occasionally, surgical procedures were not performed in these patients because they had metastatic lesions or because they were too ill to withstand such procedures. Generally, these patients did not live long enough to observe the natural history of the untreated RCC. Since the standard management of most renal masses is an immediate surgical extirpation, the natural history of these lesions has thus remained unknown. Furthermore, although the pathological findings including the tumor grade and stage provide prognostic information, the outcome for patients with RCC is occasionally unpredictable (21). Now, with the increasing number of incidental discoveries of small low-grade and stage renal tumors, the opportunities to observe the growth rate of these tumors has become possible. The data on growth rates mainly come from elderly patients or patients with complications that are too serious for them to undergo surgical procedures. A key consideration of these RCCs detected by serendipity is the nature of these lesions (10). Do these tumors progress until they threaten the life of the patients? What percentage of such RCC has an aggressive phenotype that will result in metastasis? Do patients need to have surgical operations to cure RCC that might remain dormant for decades and never become clinically evident during their lifetime? To date, there are no precise answers to these questions. However, recent publications have shed some light on these issues.

Small Incidentally Detected Renal Tumors

RCCs comprise up to 85% of all solid renal tumors (4). The widespread use of imaging modalities has now enabled us to detect small RCCs. Duchene et al. (4) indicated that in surgically treated tumors measuring 4 cm or less in size, 18 (20%) of 90 were benign tumors including oncocytoma and angiomyolipoma. It is therefore challenging for radiologists and urologists to distinguish small oncocytomas from RCC preoperatively. Small angiomyolipomas, if the components are dominantly smooth muscles, are also difficult to distinguish from RCC (12). These small benign tumors are usually treated as if they are RCC. We should keep in mind that about 20% of all small renal tumors include benign tumors. We should also keep in mind that regarding the histological classification, RCC includes several subtypes. A clear cell histology accounts for 70–80%, followed by papillary (10–15%) and chromophobe (5%) types (27).

Excellent Prognosis of Small Renal Cell Carcinoma

Hafez et al. (8) retrospectively analyzed the outcome of 485 patients with RCC treated with nephron sparing surgery. The cancer-free survival was significantly better in patients with tumors measuring 4 cm or less in size. The five-and 10-year survival rate was 99% and 94%, respectively, in 142 patients with tumors measuring 2.5 cm or less in size. Yamada et al. (31) also reported an excellent prognosis of small RCC less than 25 mm in size. Of 17 tumors, 13 were incidentally detected. All tumors demonstrated a low grade and stage, and the 10-year survival rate was 100%.
Aggressive Nature of Small Renal Cell Carcinoma

Small renal tumors smaller than 3 cm in size have long been regarded as adenomas because they seldom metastasize. In 1987, Aizawa et al. (1) reported that 7 out of 40 RCCs had metastasis including the lymph nodes, bone, and chest wall. Surprisingly, one patient with clear cell RCC measuring 8 mm in size had bone metastases and died 7 months after presentation (1). Eschwege et al. (5) showed the long-term follow-up results of patients treated with a radical nephrectomy for RCC measuring 3 cm in size or smaller. At their institute out of 850 patients who underwent a radical nephrectomy, 74 RCCs were 3 cm or smaller in size (8.7%). Ninety-three percent of the tumors were clear cell type. The average follow-up was 101 months (range 10–236). Out of the 74 patients, 11 patients died of disease progression. Five patients had metastatic disease at diagnosis. The overall cancer-specific survival rates were 81% at 5 years, and 72% at 10 and 20 years. This study suggests that clear cell type tumors measuring 3.0 cm or less in size have a potential to metastasize (5). They concluded that small RCC is not a benign disease and that there was a risk of metastatic disease. Notably, their series included only 22 incidentally detected cases (29.7%). This is in contrast with Yamada’s series, mentioned above, which demonstrated a 100% 10-year survival rate. Their series included 13 incidental cases out of 16 RCCs (81.2%). The contrast between the two series may be due to the rate of incidentally detected RCC. In fact, the lower malignant potential of incidental RCC was pointed out in another study (29). Biological differences might also exist between incidental and symptomatic RCC. Hsu et al. (10) described the pathological characteristics of 50 small RCCs measuring 3 cm in size or less. Nineteen (38%) had extension outside the renal capsule and 14 (28%) showed a high nuclear grade. Lesions measuring 3 cm in size or less and those ranging from 3 cm to 5 cm in size did not differ statistically regarding the T stage and nuclear grade. These reports all note that some small RCCs have a potentially aggressive nature when left in place.

Latent Renal Cell Carcinoma Diagnosed at Autopsy

The question remains whether small RCC may eventually cause the death of a patient if left in place. This question is analogous to occult prostate cancer discovered at autopsy. Regarding the prostate, most latent cancers are well differentiated and do not threaten the patient’s life. A report from an autopsy series by Hellsten et al. (9) before the widespread use of imaging modalities showed that about 67% of RCC remained undetected until death and that 24% of undiagnosed RCC were related to the patient’s death. This rate seems high in the era when incidentally detected RCCs are routinely found. Mindrup et al. (19) compared the rate of RCC from two periods, 1955–1960 and 1991–2001. The rate of RCC detected only at autopsy was 0.91 vs. 0.72 per 100 autopsies. The mean size of the latent RCC detected at autopsy was smaller in the more recent group, thus suggesting a better detection of latent RCC before death (19). Kihira et al. (15) reported a series of 7970 autopsies examining the histological types of RCC found incidentally and those found clinically. Of the 51 cases 25 were found at autopsy. The mean tumor size of the latent RCC was 2.6 ± 2.5 cm. This was significantly smaller than that of the clinically identified RCC (7.3 ± 2.8 cm). Grade 1 and clear cell type was more predominant in occult RCC. One case in the latent RCC had a solitary metastasis to a pulmonary hilary lymph node. This tumor was the largest latent RCC measuring 8 cm in diameter and a grade 2 clear cell type. Of note, no difference was shown between the clinical group and the latent group regarding age. This fact suggests that latent cancer might have a different character from clinical RCC. If the latent RCC is merely early small RCC, then the mean age of patients with latent RCC should be younger than the patients with clinical RCC because such tumors need time to grow. They concluded that the incidental tumors tended to have a less malignant potential (15). This finding supports the clinical observation that the age at diagnosis is lower in symptomatic patients than in patients with incidentally detected masses (18). These observations found both clinically and at autopsy do not support the concept that incidental RCCs eventually grow into symptomatic RCCs. Latent RCCs do not exhibit an aggressive nature any more at present when screening is widespread. The natural history of clinical RCCs might therefore be different from latent or incidental RCCs.

Impact of the Size on the Natural History of Renal Cell Carcinoma

Tumor size has been used to stratify the different pathological stages: pT1 (7 cm or smaller) and pT2 (larger than 7 cm). Furthermore, pT1 is subdivided into pT1a (4 cm or smaller) and pT1b (larger than 4 cm). This staging system has recently been validated in terms of the prognosis (24). Frank et al. (6) suggested a further subclassification of pT2 into pT2a (less than 10 cm) and pT2b (10 cm or greater). The larger the tumor, the more likely it will metastasize and have a poorer prognosis. Conversely, the smaller the tumor, the more likely it will be a low-grade tumor that will not metastasize. It is known that the larger lesions tend to have a higher tumor grade; however, it is not clear whether the tumor changed the grade during tumor growth or whether the tumor had a higher grade from that initially observed and thereafter had grown more rapidly.