UROONCOLOGY
Review

Treatment approaches to small renal masses in patients of advanced age (≥75 years)

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ABSTRACT

The elderly population is increasing in Turkey and across the world. With the frequent use of imaging modalities, the detection rate of coincidental small renal mass has also increased. Since small renal masses are generally not malignant, most of them can be followed up by active surveillance. In the current study, we examined the treatment options that can be offered to elderly patients with small renal masses. The optimum treatment method for patients of advanced age presenting with renal masses should be determined based on the presence of comorbidities such as age, renal function, and tumor characteristics.

Keywords: Elderly; nephrectomy; renal mass; survival

In Turkey as well as in the world, there is an increase in the older population.[1] Aging is a biological process in which the body's vitality and capacity to fulfill basic functions are gradually weakened by increasing age and consequently result in death. With the effects of aging, almost all the organs and systems undergo changes. The shrinkage of the kidneys, reduced blood flow to kidneys, lower tubular secretion and absorption ability, slower glomerular filtration rate, and a progressive loss of intact nephrons are observed in old age. Chronic renal disease is seen in approximately 26% of the population over the age of 70.[2] The World Health Organization chronologically classified old age into three categories as follows: middle aged (45-59 years old), elderly (60-74 years old), and advanced age (75 years or older).[3] It is difficult to accurately assess renal function in old age because serum creatinine alone may not demonstrate the complete renal function.[4]

At least one chronic medical problem is observed in the majority of the people older than 65, and there are a minimum of two chronic medical problems in more than 50% of those over 65.[5] Geriatric assessment should comprise not only medical but also a cognitive, social, nutritional and functional evaluation. In the literature, many studies have been conducted with elderly patients based on the age limits of 65, 70 or 75 for the treatment approach to renal masses.[6-8] For this reason, the patients should be evaluated based not only on their chronological ages, but also physiological ages and other accompanying pathologies. This will help to prevent unnecessary treatment and side effects by maintaining the profit / loss balance in the treatment plan, and avoid undesirable situations such as being untreated or receiving delayed treatment.

During the last decade, the incidence of renal tumors has increased. The most common solid lesion of the kidney is renal cell carcinoma constituting 2-3% of all cancers. It is most frequently seen in the age range of 60 to 70, and the male/female ratio is 3/2.[9] Advances in imaging technologies have led to an increased detection of non-symptomatic renal masses. Kidney tumors can now be diagnosed at a much earlier stage. The widespread use of imaging techniques and the increased life span both in Turkey and around the world have resulted in the successful identification of renal masses at a higher percentage in advanced ages.

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Small renal masses (SRMs) are defined as kidney tumors of smaller than 4 cm.[10] The grade assigned to kidney tumors provides information about the aggressiveness of the tumor and is an important determining factor for the treatment selection and potential survival.[11] The likelihood of malignancy has been shown to increase proportionally with the size of the mass.[12] Renal masses of less than 1 cm in diameter are 40% more likely to be benign whereas this percentage drops to 20 in masses of 1-2 cm.[12] The likelihood of SRMs being benign is more than 20% and the possibility of the SRM possessing aggressive features is <20%. Each 1 cm increase in tumor size is associated with a 16% increased risk of malignancy.[13] It has also been shown that as the tumor size increases, the tumor grade also increases.[13] Although the detection rate for SRMs is increasing among the elderly population, most patients may not require treatment.

With aging, the incidence of accompanying diseases also significantly increases. Therefore, in the elderly, during the process of deciding on a treatment plan, particularly for SRMs, the anticipated benefits of treatment and together with possible side effects should be evaluated. The greatest problem encountered in the treatment of SRMs is the inability to determine whether SRMs of smaller size detected at early stages have the potential to become aggressive later on, or have a benign structure and will not grow. Therefore, any prognostic information about SRMs that may initially appear to be insignificant becomes very important for the determination of an appropriate treatment approach. In this process, one of the most important tools is renal biopsy since it provides vital information both for the diagnosis and planning treatment. Renal biopsy is indicated particularly in cases where renal metastatic disease is suspected and active surveillance or ablative treatment is planned.[10]

Renal biopsy allows discrimination of benign masses that do not require treatment from progressive diseases. Performing renal biopsy before treatment has become more common due to its high sensitivity (97.5-99.7%) and specificity (96.2-99.1%) of histopathological examination. Despite the reported risks of this procedure such as hematoma, gross hematuria, retroperitoneal hemorrhage, pneumothorax, and seeding of tumor cells, these complications are not as high as have been anticipated.[10] A coaxial technique allowing multiple biopsies through a coaxial cannula should always be used to avoid potential tumour seeding.[14] The ability of renal biopsy to provide an accurate diagnosis with low morbidity and high incidence has led researchers to underline the importance of performing this procedure on all patients before planning treatment for SRMs. However, one of the major disadvantages of renal biopsy is the inability to establish a diagnosis with the procedure which varies between 0% and 47% in the literature, but it has been observed to decrease with technological developments and the increasing experience of the medical practitioners.[15-18] Important factors preventing establishment of diagnosis based on renal biopsy are the cystic nature and poor contrast enhancement of renal masses and the distance (average 13 cm) between the skin and the renal mass.[10] Furthermore, poorly differentiated tumors may include areas of necrosis and bleeding[11], which makes it difficult to make an accurate diagnosis with renal biopsy.

Another important issue is related to the agreement between the renal biopsy results and pathological findings after radical nephrectomy (RN) and partial nephrectomy (PN). The Fuhrman grading system consists of four grades ranging from 1 to 4. The agreement between biopsy and final pathological findings varies between 31 to 87.5%. However, it has been shown that the percentage of agreement is higher when grading is determined according to a binary classification system based on high and low grades.[19] In pathologic examinations, the possibility of the presence of hybrid tumors should not be disregarded. The incidence of hybrid tumors ranges from 2% to 32%.[20-23] An example is the coincidence of oncocytomas (benign) and synchronous chromophobe renal cell carcinoma for the hybrid tumors. Therefore, the presence of renal cell carcinoma cannot be ruled out by the detection of an oncocytoma in the biopsy. Furthermore, the biopsy technique also plays an important role in diagnosis. For example, a renal biopsy performed with the multi-quadrant technique has been shown to have a higher rate of detection and a lower false-positive rate for sarcomatoid patterns compared to the conventional biopsy method.[24] Advances in biopsy techniques and imaging methods will lead to more accurate results being obtained with this procedure.

The genetic and molecular characteristics of renal tumors are also important in determining the prognosis of the disease. The expression of Ki-67, p53, endothelial vascular growth factor-1 (VEGFR-1), epithelial VEGFR-1 and epithelial VEGF-D is an independent predictor of disease-free survival.[25] However, circulating tumor cells (CTCs) may be present in peripheral blood at levels of 30 to 92%. It has been reported that the patients with CTCs have more aggressive renal tumors, poorer response to treatment, and worse prognosis-free survival.[26]

The optical diagnosis technique of Optical Coherence Tomography (OCT) can distinguish normal renal parenchyma and tumor tissue based on values that indicate loss in signal intensity per milliliter using tissue-specific optical properties.[27] Another method used to diagnose renal tumors is Raman spectroscopy (RS).[28] Although neither OCT and RS are currently in routine clinical use, they present as promising methods that can be beneficial for the diagnosis and treatment of renal masses in future.

For patients with SRMs, the treatment options recommended by the Guidelines of the European Association of Urology

(EAU) include active surveillance, surgical treatment [PN/RN] and ablative treatments; e.g., cryoablation and radiofrequency ablation. Lower mortality rates have been reported in surgical treatment, but only for patients under 75 years of age.[14]

In addition, the EAU guidelines emphasize that the quality of the available data on morbidity and oncological outcomes are not sufficient to routinely recommend cryoablation and radiofrequency methods. These methods are considered to be minimally invasive but are reported to have higher local recurrence rates than those of PN. Active surveillance presents as a safer and more reliable option for the treatment of SRMs since 20% of these cases are benign, 50% are more likely to indicate a low-grade disease, and the risk of metastasis is very low (1.1%).[29] Furthermore, preoperative renal biopsy particularly in older patients prevents unnecessary surgery in 15-20% of the cases.[30,31] The higher rates of comorbidity-related mortality in patients of advanced age than deaths due to renal tumors have led researchers to question whether treatment should be undertaken for all patients.[7]

It has been reported that nephrectomy does not increase overall survival (OS) in patients with comorbidity (ies) and low tumor growth rates.[8] One of the significant problems in active surveillance is the unknown pathology of a renal mass. Therefore, performing a renal biopsy and obtaining information concerning the genetic/molecular characteristics of tissues are crucial in the selection of treatment. The risk of delayed intervention for a progressive disease is another major concern. In the active surveillance of SRMs, as reported in many studies for the safety of the patient the intervention should not be delayed for at most 14-16 months.[8]

Active surveillance is mostly preferred for cases of SRMs with comorbidity (ies), advanced age, and male patients.[8,32,33] Many studies have shown that the linear growth rate of renal masses is 0.28-0.36 cm/year, which indicates a 1-2% probability of progression to a metastatic disease.[34,35] This suggests that through regular monitoring of the patients under active surveillance, treatment can be successfully implemented without the disease progressing or negatively affecting the survival rate. A large multicenter non-randomized trial reported the 5-year cancer-specific survival to be 99% and 100% following primary treatment and active surveillance, respectively.[8]

There is no standard for the imaging methods to be used during patient follow-up and the available methods cannot differentiate between silent and aggressive renal masses. In elderly patients with a Charlson comorbidity index of >2, the complication rate increases approximately two-fold regardless of the type of surgical treatment.[36]

Although ablative therapy has shown favorable results in the medium-term, its long-term outcomes are not available yet. The complication rates reported (3%) are lower than those for surgical treatments (7%).[37,38] Tumor size and location are important in selecting the type of ablative therapy. The absence of renal ischemia makes ablative therapy more advantageous than surgical treatments in preserving renal function.[39,40] However, the oncological outcomes have been found to be worse than RN and PN. With technological advances, ablative therapy may provide more successful outcomes for SRMs and it will become a more favorable treatment option in the future.

According to the SEER Medicare data, patients with a clinically confirmed pathological T1a tumor showed that 9% to 10% of these patients preferred non-surgical treatment and the percentage of non-surgical treatment increased from 7.5 to 18.6 between the years 2000 and 2010.[41,42] This increase was found to be higher in older people.

It has been shown that in early stage renal tumors, PN has better OS and cancer-specific survival (CSS) than RN.[7] This has been attributed to increased mortality rates after RN related to surgical and cardiovascular etiologies. It has also been reported that renal function is decreased due to the reduced number of renal units/nephrons after RN, which in turn increases rates of cardiovascular mortality in the elderly.[43]

Every 1 cm increase in the size of renal tumor results in a 47% reduction in the rate of performing PN.[10] In addition, high comorbidity, female gender, and surgeons' belief that PN has higher complication rate may be considered as reasons for PN being a less favorable option. However, many factors such as the patient's educational, sociocultural and income levels and health insurance status can play a role in the selection of treatment. Laparoscopic PN is technically more difficult than open PN and it has a higher short-term complication rate.[44,45]

Chronic kidney disease (CKD) is more frequently seen after RN treatment than PN treatment. Cancer-related mortality rates are also higher in patients with CKD. Preoperative renal dysfunction has been shown to reduce OS in patients that underwent PN and RN.[7] In recent studies it has become controversial whether PN is more advantageous over RN in terms of OS. PN has been associated with better survival rates in patients younger than 65 years, but this effect is not observed at older ages.[6]

The etiology of CKD is important and it is emphasized that CKDs differ as for medical or surgical indications. After RN or PN, glomerular filtration rates decrease. A comparative study performed with healthy group and a donor nephrectomy group with a 30-year follow-up showed that the OS rates of both groups were similar.[46] The EORTC study also showed that RN and PN

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resulted in similar OS rates; however, another study reported that PN is not a better option in terms of OS in elderly patients.[6]

The EAU Guidelines recommend PN in cases of large renal masses (T1b). This may also apply to elderly patients, but recent studies have shown that, in particular, RN has no advantage concerning OS. PN maintains better renal function than RN, but OS does not improve with the application of PN, especially in elderly patients. A significant reason for this situation is that the most common cause of death in patients over 75 years receiving active treatment is cardiovascular diseases.

In a study that evaluated the treatments performed on elderly patients with a T1a renal mass between 2000 and 2010, RN was found to be the most common treatment in the 75-84 age group whereas non-operative treatment/surveillance was the most preferred method for those over the age of 85.[47] Furthermore, the percentage of RN in the 75-85 age group gradually decreased over the study period, but there was a gradual increase in PN for the same period.[41]

In elderly patients, nomograms have been used to calculate mortality.[47] Nomograms allow scoring cases based on the evaluation of patient characteristics and other criteria such as climbing stairs, undertaking daily activities and performing financial transactions to calculate the probability of mortality using the total score. A mortality calculation can assist in choosing the appropriate treatment for each patient.

In recent years, the increasing use of PN and other nephron-protective treatments has led to a significant decline in the rates of RN.[10] Laparoscopic RN began to be performed in the 1990s and has been shown to have similar oncological outcomes and better postoperative parameters compared to open RN.[10] Young age, female gender, less complex renal masses, and lower mortality rates have been associated with increased percentages of minimally invasive surgery.[48] Robot-assisted laparoscopic RN (RALRN) has similar oncological, but better perioperative outcomes than open RN but it is a more expensive treatment option.[10] RALRN is less advantageous than laparoscopic RN but it is particularly preferred for T1b or larger tumors.[10] On the other hand, the growing experience in robotic approach has allowed performing RPN for larger and complex tumors.[49] Several suggestions have been made in order to reduce the renal ischemic injury and preserve the renal function, including renorrhaphy, and robotic surgery which may allow faster tumor resection, and selective application of PN without renal arterial clamping.

In conclusion, the ideal treatment for renal masses in elderly patients should be determined based on the evaluation of criteria such as comorbidity (ies), patient age, renal function, and tumor characteristics.

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