Renal cell cancer—a multimodal approach to preserving renal function and improving survival

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Introduction

Renal cancer comprises ~3% of all malignancies and in the past decade, the incidence has grown from 2.3 to 4.3% per year [1]. In Germany, the estimated number of newly diagnosed cases of renal cell cancer is 21.3 per 100 000 for men and 10 per 100 000 for women [2]. Renal cell cancer accounts for the top 10 cancer-associated mortalities in the Western world [3]. The size of renal cancer tumours has decreased in the past decade mainly due to the widespread use of ultrasonography [4, 5]. Within the past 10 years, tumour size at initial diagnosis has decreased from 4.1 cm in 1998 to 3.1 cm in 2008. In addition, the majority of patients diagnosed with renal cell cancer are in the 70+ to 85 age group, with considerable comorbidity [3]. Despite early diagnosis and a smaller tumor size, the overall survival in patients with renal cell cancer has not improved significantly in the past years. In contrast to other parenchymal malignancies, reduction of organ mass in renal cell cancer and the partial loss of renal function influence the survival of patients with kidney-associated malignancy considerably [6].

Surgical therapy for renal cell cancer—the concept of ‘nephron-sparing surgery’

What are the treatment options for renal cell cancer? The classic concept of radical nephrectomy, including removal of the ipsilateral adrenal gland and lymph nodes within Gerota’s fascia was introduced by Robson [7] in the mid-60s. The concept of partial nephrectomy, also called nephron-sparing surgery, has emerged from developments that have taken place in the past 10 years [8–12]. Several studies have shown that the rate of survival associated with resection of a localized renal mass is similar to the survival rate of patients who undergo radical nephrectomy [13]. A more recent study showed that the survival after partial nephrectomy for pT1b (<7 cm) renal cell cancer was similar to the survival rate for radical nephrectomy [14]. This is

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of particular note since some renal tumours initially diagnosed as malignant, are benign or semi-malignant tumours, which are resected at the expense of a significant loss of renal mass. Another study by the Cleveland Clinic shows that the overall survival rate and cancer-specific survival rate is significantly higher in patients with partial nephrectomy. In addition, postoperative renal function significantly impacted the survival of renal cancer patients up to 96 months after surgery [15]. Although the cancer survival rate of patients who undergo nephron-sparing surgery is similar to the survival rate of those who undergo radical nephrectomy, nephron-sparing surgery is not very common. This is of particular note since modern techniques such as laparoscopy and the da Vinci device used in nephron-sparing surgery have existed for several years and the rate of complications for open versus endoscopic kidney surgery are similar [12, 16]. For example, the SEER registry reports that only 20% of patients with an initial tumour size of 2–4 cm undergo partial nephrectomy [13]. Recently published guidelines by Novick et al. [17] and others introduce nephron-sparing surgery as an equivalent surgical option of renal cancer although a direct comparison has not been done. At our institution, ~90% of renal cell cancer patients undergo nephron-sparing surgery. Even multilocular renal cell cancers can often be resected without radical nephrectomy.

Why is the kidney vulnerable to mass reduction?

Since the majority of renal cancer patients are older, it is necessary to further elucidate this question. Like any other organ, the kidneys undergo a certain process of senescence. This includes subcellular structural changes with brush border abnormalities and mitochondrial changes. Other hallmarks are telomere shortening with increasing oxidative stress and the accumulation of advanced glycosylation end products with direct renal toxicity [18].

Cross-sectional studies show that a decline in glomerular filtration rate progresses with age and this is associated with increasing mean arterial blood pressure [19, 20]. The structural hallmarks of these findings are glomerulosclerosis and afferent arteriolar wall thickening [21]. Functional changes of the ageing kidney comprise a considerably reduced renal functional reserve capacity after maximal vasodilating stimuli [22]. Furthermore, in elderly patients, renal vasculature exhibits increased renal vascular resistance, which is particularly sensitive to the stimulation with angiotensin 2 and to sympathetic nerve activity [23]. These functional changes are paralleled by impaired renal sodium haemostasis and a loss in the ability to concentrate or dilute urine [24]. The latter can accentuate dehydration in the elderly. The size of the kidney increases until age 40–50 and then decreases with age [25]. Many of these changes are due to tubulointerstitial changes, including interstitial fibrosis and fibrosis rather than just loss of glomeruli. There is also an increase in interstitial volume associated with interstitial fibrosis. In experimental models of the ageing kidney, collagen deposition is increased in association with age-related expression of fibrosis-related genes [26]. However, the clinical significance of these changes in the ageing kidney is mostly negligible unless an acute or chronic illness (e.g. radical nephrectomy for renal cancer) further impairs renal reserve.

Despite the natural course of kidney ageing, the prevalence of renal diseases in older patients is higher. Primary renal diseases of glomerular origin have a 2- to 3-fold increased prevalence compared to younger patients [27]. Glomerular diseases include a 4-fold increase in membranous nephropathy, crescentic glomerulonephritis and amyloidosis. With regard to other associated diseases, diabetes produces several changes in the kidney, including glomerulosclerosis and arteriolosclerosis. Infection, particularly ascending infection, is more common with increasing age, as both a decline in immune function and associated pathology predisposing the patient to infection, such as obstructive uropathy, become more common.

The prevalence of hypertension increases with age and there is a complex relationship between renal function and blood pressure regulation. It is assumed that the reduction of nephron mass may influence the prevalence and severity of hypertension after nephrectomy [28]. Blood pressure is of particular importance since medical treatment of metastatic kidney cancer with tyrosin kinase inhibitors may induce hypertension.

The impact of renal function on survival

Renal function substantially affects cardiovascular and overall survival [29, 30]. Even a mild reduction in glomerular filtration rate should be considered a major risk factor for cardiovascular complications after myocardial infarction [20]. The reduction of a nephron mass, e.g. radical nephrectomy, is associated with a fall in glomerular filtration rate. In living-related kidney donations, a meta-analysis showed a fall in glomerular filtration rate (GFR) of 17 mL/min within 1 year after nephrectomy [31]. It is of note, however, that living donors followed over a long period of time showed an increase in GFR of 1.4 mL/min per decade. The recovery of renal function in donor kidney nephrectomy has an impact on long-term survival. Studies from Scandinavia found no difference in the overall survival rate for post-donor nephrectomies [32]. Why does donor nephrectomy differ from radical nephrectomy in regard to renal cancer in terms of GFR? We compared the initial S-creatinine of 231 kidney donors from the Transplant Centre in Heidelberg with the S-creatinine of patients prior to radical nephrectomy [33]. The median S-creatinine of the kidney donors was 0.81 ± 0.19 (71 ± 17 μmol/L) with a S-creatinine of 0.7 (62 μmol/L) at the 25th percentile and 0.9 (79 μmol/L) at the 75th percentile. In contrast, the majority of patients (cited in reference 33) had an S-creatinine of >1.18 (104) and a considerable number of patients had values >1.4 mg/dL (123 μmol/L). Although there are no formal GFR values available, it is plausible that the pre-nephrectomy GFR in renal cancer patients was significantly lower compared to our kidney donor cohort. In a retrospective cohort analysis, Huang et al. also found that the extent of renal mass reduction (e.g. nephron-sparing surgery versus total nephrectomy) has an important impact on long-term renal function. When a total nephrectomy for
renal cancer was performed, the hazard ratio for developing GFR < 60 mL/min was 3.82 and for GFR < 45 mL/min, it was 11.8 within 3 years of follow-up [23].

Conclusion

Renal function is an important indicator for survival in renal cell cancer patients. The type of surgery (nephron-sparing versus radical nephrectomy) marks the most important difference. Medical treatment of metastatic kidney cancer is emerging with promising results. The diagnosis and treatment of chronic renal failure after renal cancer surgery, the surveillance of renal function with adaptation of various drugs to impaired renal function brings the nephrologist together with a team of specialists taking care of this group of patients. We would expect that such a multimodal approach will increase the survival rate, which is associated with a better quality of life in patients with renal cell carcinoma.

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References


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