

What is the Optimal Management Strategy for Multifocal and Hereditary Kidney Cancer?

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Introduction

Multifocal kidney cancer presents unique challenges for treating physicians. After the initial radiologic, genetic and interventional evaluation to determine the etiology of the tumors, the appropriate extirpative strategy must be identified. Historically, total nephrectomy and hemodialysis with possible renal transplant later was the primary therapeutic strategy for these patients. Later, as partial nephrectomy techniques were developed, nephron sparing surgical (NSS) approaches became the standard of care for patients presenting with multifocal and hereditary renal cell carcinoma (RCC) conditions. Retaining functional native renal parenchyma in the face of multifocal RCC is not without risk however. Surgery to remove multiple renal tumors simultaneously requires alteration of standard surgical techniques and consequently produce different perioperative outcomes [1] and increased risk of complications [2,3]. Due to these differences in technique and outcomes, the term multiplex partial nephrectomy (MxPNx) has been coined to denote these differences [1,4]. Furthermore, after initial multi-tumor partial nephrectomy, recurrent ipsilateral renal tumors may arise necessitating repeat and salvage renal surgery (RRS and SRS). These repeat partial nephrectomies, while highly successful in preserving native renal function, are highly morbid with complications rates exceeding 50% [5-8]. In addition, these procedures may be required at a median of every 6 years [9].

Keywords: Hereditary cancer syndromes; Renal cell carcinoma; Cancer therapy; Disease management; Urologic oncology

Alternative Strategies

The alternative to multiple complex and morbid renal surgeries for multifocal RCC—renal transplant—have improved immensely over the past few decades, with 5-year patient survival rates as high as 91% [10]. On the other hand, dialysis patients have a life expectancy that is 9.8 years shorter than transplant recipients [11]. Additionally, allograft survival is also improving. McCullough et al. determined that graft survival from 2000-2005 was significantly higher than from 1994-1999, with 81% of living donor grafts surviving 5 years, and 58% of

living donor grafts surviving 10 years. Chang et al. reported the allograft half-life to be as high as 16 in some patient subgroups [12]. The improvement in graft survival is largely due to an increased understanding of immunosuppression [13]. While these statistics are promising, it is important to note that these were studies of patients predominantly with medical end-stage renal disease (ESRD) with concomitant comorbidities such as diabetes mellitus, hypertension and hyperlipidemia. Chronic kidney disease (CKD) and ESRD due to surgery, as seen in some patients with hereditary or multifocal kidney cancer, has a different natural history [14] than ESRD due to medical renal disease [15]. Patients with hereditary and multifocal RCC tend to be younger and healthier [16] than the average patient on dialysis with ESRD due to medical renal disease and the relative lack of those comorbidities almost certainly affects the applicability of these data to this patient population.

As transplant outcomes continue to improve, and hospital systems and insurers increasingly focus on complications and spiraling costs of care, [17] the continued economic feasibility of current surgery-based approaches for multifocal RCC must be reconsidered. Agochukwu et al. using Medicare reimbursement rates, estimated the accumulated cost of uncomplicated completion nephrectomy, fistula placement, and dialysis to be just under \$200,000 at 5 years post nephrectomy [18]. In this analysis the cost of dialysis was intentionally underestimated for the model between \$40,000 and \$50,000 per year. On the other hand, Nassir et al., using US Medicare claims, determined the mean cost of renal transplant to be just over \$65,000 [19]. Agochukwu et al. also compared the cost of SRS in a solitary kidney to the cost of nephrectomy and dialysis. This modeling indicated that a financial benefit of repeat partial nephrectomy was reached at 0.68 years when compared to the hypothetical cohort of patients undergoing uncomplicated total nephrectomy, fistula placement, and dialysis. Even when the cost of salvage partial nephrectomy was over-estimated—to account for the high complication rate—the financial benefit was reached within one year [18]. Comparing these two studies suggests RRS and renal transplant are economically favorable to total nephrectomy and dialysis, but the greatest obstacle to renal transplant becoming a reasonable treatment option in multifocal RCC continues to be organ availability.

Donor kidney shortage has been a problem for decades. However, thanks in part to the kidney exchange program and extended donor criteria, the median wait time for any donor was 4.5 years in 2009. Despite the success of these kidney exchange programs, this still represents a 50% increase in wait time from the 3 year wait in 2003 [20,21]. The increased demand is due to an increasing number of patients on the waitlist and an unchanged donation rate. The number of patients on the waiting list doubled from 2003 to 2013, with diabetes being the most common and fastest increasing cause of ESRD. Additionally, more and more kidneys are being rejected due to donor diabetes [10,20]. Consequently, despite marked improvements in immunosuppression tolerability, graft survival, and related transplant outcomes, RRS continues to be the gold standard treatment of choice for multifocal and hereditary RCC despite the well-documented high rate of peri- and post-operative complications.

Conclusion and Outcomes

As complications and hospital re-admissions continue to gain prominence at an administrative level, the improving outcomes and longevity of transplant allografts along with decreasing costs of peri- and post-transplant care and dialysis make this approach an increasingly attractive treatment option for patients with multifocal and hereditary RCC. However, widespread adoption of this transplant strategy is not reasonable due to extremely limited organ availability. Currently, the standard of care for multifocal RCC is initial, repeat and salvage multiplex partial nephrectomy but this strategy is increasingly unappealing due to high complication rates and prolonged hospital admissions. With the skyrocketing incidence of obesity and diabetes nationally, the current shortage of available transplantable kidneys shows no signs of improving; and, thus, prevents bilateral nephrectomy and transplant from being a feasible option for patients with bilateral multifocal and hereditary kidney cancer. Consequently, at present, MxPNx, repeat and salvage partial nephrectomy continue to have a primary role in the treatment of hereditary and multifocal RCC.

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