Review Article

Can Renal Denervation during Nephron Sparing Surgery for Renal Cell Carcinoma Prevent De Novo Hypertension Occurrence and Potentially Confer a Survival Benefit?

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Abstract

Technological advances, including laparoscopic and robotic surgery and diagnostic imaging, seem to have improved renal functional and oncological outcomes in patients undergoing nephron-sparing surgery. There is Level 1 evidence that nephron-sparing surgery is not superior to radical nephrectomy in terms of overall and cancer-specific survival; however, the indications for nephron-sparing surgery to treat renal cell carcinoma are expanding without substantive supportive evidence, and the updated guidelines accept that radical nephrectomy should not be used when nephron-sparing procedures are possible. Hypertension that develops after nephron-sparing surgery is suspected to play a significant role in the survival benefit; therefore, there is a room to improve nephron-sparing surgery. Further efforts are necessary to achieve better survival, e.g., the procedure should be modified to prevent postoperative hypertension. Hereby, "renal denervation during nephron-sparing surgery" appears to minimize hypertensive complications after nephron-sparing surgery; therefore, more attention should be paid to preventing de novo hypertension in patients undergoing nephron-sparing surgery.

Introduction

Partial Nephrectomy (PN) was first introduced to excise localized Renal Cell Carcinoma (RCC) while leaving a surrounding area of normal renal parenchyma [1]. In the early 1990s, PN, or Nephron Sparing Surgery (NSS), has been popularized for treating patients with RCC whose functioning renal parenchyma must be preserved. Its surgical techniques have improved with novel, expanded indications, along with the advent of sophisticated diagnostic imaging modalities [2]. Classically, NSS has been "imperatively or absolutely" indicated for patients with RCC for whom Radical Nephrectomy (RN) would render the patient anephric, resulting in subsequent dialysis [3]. Another "relative" indication has been proposed in patients with unilateral RCC and a functioning contralateral kidney, especially when the opposite kidney is affected by an impending condition that might threaten its future function. In addition, NSS has been "electively" indicated in patients with unilateral localized RCC and a normal contralateral kidney, and there is special concern for the remaining kidney being at risk for future dysfunction. State-of-the-art imaging technologies, including Computed Tomography (CT) and ultrasound sonography, led to an increase in identifying incidental small RCCs [4,5]. Patients with a single, small, unilateral, localized RCC may be considered suitable candidates for elective NSS even when the opposite kidney is completely normal [6]. In the new millennium, this "elective" indication has gained gradual acceptance, and several studies have demonstrated the successful use of electively indicated NSS, demonstrating the short-term and long-term favorable results of elective NSS for cancer control and the apparently recognized renal functional benefits of this approach.

Background

Usually, cases of localized tumors that are easily amenable to NSS raise controversy over whether NSS is indicated for patients with a normally functioning contralateral kidney. Despite encouraging results obtained with NSS when treating patients with this indication, fear of renal fossa recurrence and subsequent metastasis, along with considerable perioperative complications, has kept RN as the gold standard for treatment of this indication since the landmark Robson study in 1969 [7]. Surveying the AUA membership (2011) shows that there is considerable heterogeneity in the trends of treating patients with clinical T1a tumors [8]. As NSS is often selected for tumors at the renal pole, academic urologists are less likely to choose nephrectomy, and many urologists continue to perform nephrectomy when tumors are larger or more centrally located [8].

The overall evidence from meta-analyses (6 randomized controlled trials and 28 non-randomized studies) suggests either equivalent or better survival with PN compared with RN [9,10]. Laparoscopic RN offers an equivalent survival to open RN, and all laparoscopic approaches achieve equivalent survival. PN results in significantly better preservation of renal function than does RN, regardless of the choice of approach or technique [9-11]. Despite the most flagrant violation of Robson's concepts (incomplete tumor excision, local recurrence, ignorance of microscopic satellite tumors and multifocality) of a "radical" tumor nephrectomy, PN (deliberate opening Gerota's fascia, freeing the kidney from surrounding fatty tissue, and resecting the tumor alone) remains an important treatment option for renal mass patients because the oncological efficacy is comparable to that of RN and the risk of chronic kidney disease is significantly reduced; still, the impact on the quality of life and overall survival requires continued investigation [12,13]. Even small renal tumors may include aggressive types, but we have always considered the presence of such aggressive RCCs, except for those that are labeled as rare and exceptional as follows. Advanced tumor stage (pT3) was found in 3.0%, 5.1% and 12.1% of cases in the 2, 3 and 4-cm groups; grade 3 was noted in 7.1%, 9.0% and 14.0%; metastases at diagnosis were identified in 3.0%, 2.6% and 6.0%; multifocality was present in 29 patients (5.3%) and its rates were 2.0%, 5.1% and 7.05% in the 2, 3 and 4-cm groups, respectively [14]. Negative prognostic features as well as worse oncological outcomes increase with a tumor diameter above 2 cm. These data have important implications when considering active surveillance of small renal tumors [15]. New diagnostic tests are warranted to better stratify patients with respect to treatment aggressiveness for small incidental renal tumors [14].

The EORTC (European Organization for Research and Treatment of Cancer) randomized controlled trial 30904 showed that renal dysfunction was only significant for moderate renal disease (eGFR 30-60 ml/min/1.73m^2) and was similar in terms of advanced dysfunction and renal failure between the RN and NSS groups. The advantage in terms of renal function preservation for the NSS arm did not translate to a better overall survival at a median follow-up of 9.3 years. The expanding indications are still without substantive supportive evidence, and we have Level 1 evidence that PN is not superior to RN in terms of the overall and cancer-specific survival [12,16,17]. Clearly, the study challenges the better overall survival attributed to NSS by preservation of kidney function [17,18]. The increase in moderate chronic kidney disease among RN patients was not associated with a corresponding reduction in the survival, which was most likely because the adjusted hazard ratios for death were 1.2 and 1.8 for patients with eGFRs of 45-59 and 30-44, respectively [19]. Thompson reconciled this by considering that "surgically" induced chronic kidney disease (i.e., nephrectomy) may not have the same negative health impact as "medically" induced chronic kidney disease (i.e., long-standing diabetes or hypertension) [13]. Laguna and associates also commented that preoperative cardiovascular comorbidity was similar in the RN and NSS arms, but no information on the diabetes or hypertension incidence was provided. Both conditions are well-known "medical" causes of renal dysfunction [20]. The limitations of this randomized controlled trial were hastily described, but it is unlikely that they exceed the limitations of systematic reviews and meta-analyses of observational/retrospective studies (specific methodological limitations with selection biases). In waiting for dismissal or confirmation of the overall survival effect of

NSS, any attempt to minimize the possibility of "surgically" induced renal dysfunction seems reasonable [20]. Therefore, the procedure of NSS needs to be reviewed with consideration for what contributes to the survival benefit, and it should be modified to increase overall survival; therefore, in this communication, we focus on the occurrence of hypertension after NSS.

Discussion

Hypertension is reported in 14% to 35% of patients with RCC who present with paraneoplastic syndrome [21]. Hypertension is a significant risk factor for RCC [22]. There is sufficient evidence demonstrating that hypertension predisposes to RCC development. Most studies have reported an association with a history of long-term hypertension, and cohort studies with blood pressure measurements taken at baseline have generally reported a dose-response of increasing risk with rising blood pressure level [23-26]. The biological mechanism underlying the relationship between elevated blood pressure and increased risk of RCC remains unknown. One theory suggests that the chronic renal hypoxia accompanying hypertension promotes tumor cell proliferation and angiogenesis by a transcription factor known as hypoxia inducible factor [27]. Subtle changes in renal function prior to clinical hypertension may make the kidney more susceptible to carcinogenesis, and some angiogenic and other growth factors that are involved in hypertension may also participate in renal carcinogenesis and progression [28]. As in individuals with elevated BMI, patients with essential hypertension also exhibit increased lipid peroxidation, which has also been implicated in the pathogenesis of RCC [29].

Although 70% of RCCs are radiographically hypervascular, Arteriovenous Fistulae (AVF) is rare entities [30]. Hypertension in these cases may be due to increased cardiac output or increased renin secretion secondary to ischemia distal to the fistula [31]. Interestingly, 70% of those with clinically significant AVF and RCC are female. In these cases, resolution of hypertension after nephrectomy is common [32,33]. Hypertension can occur because of ischemia secondary to venous shunting of blood away from the affected area. Renin-mediated hypertension occurs secondary to relative renal ischemia that is distal to the fistula (A-V fistula associated with RCC). Stojanovic and associates reported that hypertension was resolved after nephrectomy in 24 patients with RCC, suggesting that RCC may cause arterial hypertension [34]. According to the comparison to hypertension *versus* RCC, RCC causes hypertension and vice versa in selected cases; however, nobody is puzzled by the chicken or egg causality dilemma.

Hypothetically, reduced blood flow and glomerular pressure in the partially resected kidney could cause renin release, ensuring the Goldblatt model of hypertension persists [35]. Several sporadic reports have indicated that PN [36,37] or nephrolithotomy [38] may precipitate postoperative hypertension and renal injury due to trauma can lead to postoperative hypertension in the form of "Page kidney" after repair [35]. Lawrentschuk and colleagues (2012) claimed that PN does not cause postoperative hypertension in 48 patients undergoing PN over 2 years [35], while Inoue and colleagues showed that hypertension progressed after PN (79 patients) compared with nephrectomy (24 patients) over 9 months [39]. The study by Inoue and associates seems to be the first report showing the effects of

PN *versus* RN on blood pressure; therefore, there is no previously published report showing that PN cures hypertension in hypertensive patients with RCC.

The World Health Organization rates hypertension as one of the most important causes of premature death worldwide. One of the key risk factors for cardiovascular disease is hypertension, which already affects one billion people worldwide, leading to heart attacks and strokes [40]. Therefore, attention should be paid to hypertension and renal function after PN, especially in terms of evaluating clinical benefit in the comparison between PN and RN.

Renal denervation is a therapy that targets treatment-resistant hypertension. The extent of renal denervation required to reduce blood pressure has yet to be established, and the possibility that inadequate denervation could exacerbate hypertension must be considered. Even if renal denervation is successful in lowering blood pressure, would this translate to improved cardiovascular outcomes? Or would there be significant trade-offs? Renal denervation is an interesting idea that merits further study. Small groups of patients may benefit; however, ablation of renal nerves as a treatment for high blood pressure appears to be more of a sacrifice bunt than a home run [41].

Recently, the R.E.N.A.L. nephrometry scoring system was introduced to objectively describe renal masses with respect to the size, degree to which they are exo/endophytic, nearness to the collecting system, and location relative to polar lines as well as whether they are anterior or posterior. The R.E.N.A.L. nephrometry scoring system may be able to predict functional renal loss attributed to NSS [42]. Nephrometry systems achieve two primary goals, methodological analysis of the tumor location and standardization for reporting of tumor data. The secondary goals of nephrometry scoring are to predict success of PN, risk of postoperative complications, and functional and oncologic outcomes.

Currently, the 2016 National Comprehensive Cancer Network (NCCN) guideline recommends NSS for a T1a renal mass, stating that RN should not be used when nephron-sparing procedures are possible [43]. Additionally, EAU guidelines 2016 summarized the evidence as follows: laparoscopic RN has lower morbidity than open surgery (LE 1b); oncological outcomes for T1-T2a tumors are equivalent between laparoscopic and open RN (LE 2a); and PN can be performed, either with an open, pure laparoscopic or robot-assisted approach, based on surgeon's expertise and skills. The EAU recommends that RN not be performed in patients with T1 tumors for whom PN is indicated [44]. Therefore, open NSS is the gold standard treatment of T1 renal cell cancer. In experienced centers, the laparoscopic or robot-assisted approach is a viable alternative. A routine goal during NSS should be the concept of the trifecta, which involves reaching the following three key outcome criteria at once: a negative cancer margin, no or a minimal decrease in renal function, and no surgical complications [45]. To preserve postoperative renal function, it is important to develop techniques that minimize renal ischemia times, which include renal hypothermia, the early unclamping technique, segmental artery clamping, and the zero-ischemia technique [45]. The unclamped procedure does not usually skeletonize the renal artery, while clamped procedure isolates the renal pedicle and unintentionally or inadvertently denervates tissue around the renal artery.

Conclusion

In conclusion, technological advances in NSS have minimized perioperative complications and improved renal functional and oncologic outcomes in the long term. However, there remains room for improvement, and further efforts are necessary to achieve the ultimate outcome trifecta. Here, we would like to expand the trifecta to the "quadfecta" by adding "renal denervation" to minimize hypertensive complications after NSS. Renal denervation for hypertension is not yet a well-established procedure; therefore, we recommend at least including "with or without renal denervation" as an evaluation criteria for the clinical study of NSS in RCC. The work to be done first is to try to gather objective data regarding the de novo occurrence of hypertension after NSS and after RN; thereafter, hopefully someone will prove our hypothesis in the near future.

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