The global burden of kidney cancer: a call to action

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Running title: Global burden of kidney cancer

Word count: 1999

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Introduction

There are more than 338,000 new cases of kidney cancer worldwide each year with an estimated 22% increase by 2020.[1] The most frequent type of kidney cancer is renal cell carcinoma (RCC) which represents over 90% of all renal malignancies.[2] As the population ages and the prevalence of known risk factors such as obesity and hypertension increases, one predicts a growing global burden from kidney cancer. Between 1980-2014, over 420,000 people died of kidney cancer in the US, and cancer mortality for kidney cancer patients remained unchanged [3]. At least 20% of patients present with metastatic disease (mRCC) and another 10-20% of patients undergoing potentially curative surgery develop metastases.[4] Deteriorating health-related quality of life (HRQOL) with tumor burden along with the impact of treatment-related side-effects are substantial.[5] Most mRCC patients eventually die even if they have access to newer and very expensive systemic therapies and despite initial responses often associated with significant toxicity.[6] Increased imaging has improved detection of small renal masses but with an increased risk of overtreatment of benign or low grade malignancy renal masses, often in older patients with comorbidity. The estimated number of surgically removed misdiagnosed benign renal masses in the United States increased by 82% from 2000 to 2009. Strategies to prevent over-treatment with unnecessary costs are needed.[7] Follow-up schemes after surgery are not standardized, are costly and have limited evidence of overall benefit.[8] There are marked variations in incidence and mortality that can inform us about risk factors and patterns of health care. Further research is needed to understand the impact of all these factors on the burden of RCC. The aim of this commentary is to stimulate awareness of the growing global burden of kidney cancer including the risk factors and the challenges that clinicians currently face in diagnosis and management.

Disparity in incidence and mortality

The incidence rates of kidney cancer are still rising in most countries of the world. The gap in mortality rate between emerging and developing economies appears to be widening.[9] The explanation for the international variations in incidence and mortality of kidney cancer is probably a combination of genetic variations unique to ethnic and regional populations and lifestyle/environmental factors coupled with availability of healthcare resources for imaging, variable treatment options, skilled healthcare professionals, and incomplete RCC data in countries where investment is needed in cancer reporting.[9]

Despite the increasing incidence of kidney cancer, the causes are poorly understood. Inherited genetic predisposition is likely underestimated. RCC can develop within certain syndromes of which von Hippel-Lindau is the most common.[2] Cigarette smoking, obesity and hypertension are the most established modifiable risk factors for RCC with an increasing prevalence in the general population. Cigarette smoking increases the risk of RCC by 54% in male and 22% in female smokers [10], and 5 kg/m^2 increments in body mass index increase the risk of RCC by 24% in men and 34% in women.[11] Uncontrolled elevated systolic (≥160 mm Hg) and diastolic (≥ 100 mm Hg) blood pressure is associated with a two- or threefold increased risk of RCC.[12] Long-term dialysis in patients with renal failure is also associated with higher risk of RCC.[13] More research is needed to establish the underlying mechanisms linking these risk factors to RCC and to develop prevention strategies. A more focused education of physicians is necessary to raise awareness of the risk factors of kidney cancer.

Diagnosis

Clear cell RCC (ccRCC), which is the most common histological subtype, accounts for approximately 75% of RCC.[2] There are currently no recommended screening tests for kidney cancer among asymptomatic individuals in the general population. Identification of a high-risk population may allow a pilot study to determine whether a screening program could affect survival in RCC.[14] Aquaporin-1 and perilipin-2 hold promise as diagnostic and screening urinary biomarkers for clear cell or papillary RCC and in the differential diagnosis of imaged small renal masses (SRMs).[15] The diagnosis of RCC may be delayed because most renal tumors remain asymptomatic until at least locally advanced. The classic presentation with the triad of flank pain, gross hematuria, and palpable abdominal mass is now rare in developed countries (6-10%) but is still common in the developing world and reflect advanced stage and often aggressive histology with lower cure rates. Potentially misleading paraneoplastic syndromes including fever and night sweats are found in approximately 30% of patients with symptomatic RCCs. In more developed economies, the majority of renal masses are detected incidentally by abdominal ultrasound or computed tomography performed for other medical reasons. Magnetic resonance imaging (MRI) is rarely of additional diagnostic use but may aid staging.[16] In most cases an accurate diagnosis of RCC is possible by imaging alone. However, on final pathologic review after surgery 20-40% of the SRMs are benign and thus overtreatment is a great concern.[7] Therefore percutaneous renal tumor biopsy (RTB) which provides histopathological confirmation of RCC is recommended in select patients with SRMs prior to treatment. RTB can also be recommended in patients with mRCC to select the most suitable form of treatment.[16] Newer imaging modalities such as molecular imaging, perfusion/diffusion MRI and radiomics show great promise in revealing histologic diagnosis of renal tumors and could ultimately replace RTB, which remains an invasive procedure.[17] All these techniques are expensive approaches

unavailable to most centers. In contrast, according to the World Health Organization, up to two-thirds of the world population have no access to even simple diagnostic imaging.

Global burden of treatment

There is great disparity in availability of different treatments, particularly for the early stages when tumors are smaller and cure is possible by resection. Surgery is the gold standard for the management of SRMs or clinically localized renal masses suspicious for RCC. Within the past decade there has been a shift from radical nephrectomy (RN) towards increased use of nephron-sparing surgery [partial nephrectomy (PN)] in developed countries.[18] The burden of complications after surgery is associated with age and comorbidity status.[19] PN performed by laparoscopy or robotic-assisted laparoscopy and ablation techniques have not been widely adopted in low-resource countries due to the need of additional hospital resources, skilled professionals, and multi-specialty care. Even active surveillance may involve additional resources, in view of the need for regular follow-up, and availability of suitable imaging and biopsy modalities.[20] Cost comparisons of the different treatments are highly variable in different health care systems. Treatment costs of SRMs were found to be lowest for active surveillance, followed by ablation, minimally invasive RN, minimally invasive PN, open PN and open RN.[21] There is also a need for standardized surveillance strategies after surgery that limit unnecessary cost and radiation exposure without compromising cancer control.[8]

Open RN remains the standard of care for locally advanced RCC when the tumor is expected to be completely resectable. Systematic adrenalectomy or extensive lymph node dissection (LND) is not recommended when abdominal CT shows no evidence of lymph node or adrenal involvement.[22] Neoadjuvant and adjuvant medical treatments in these patients should be further investigated.[23]

In the last 10 years, cytokine-based immunotherapies (interferon-α and high-dose interleukin-2) for advanced/metastatic RCC have been superseded by targeted drugs demonstrating a higher overall response rate and a more favorable safety profile. Several targeted agents are currently approved in the US and Europe for the treatment of mRCC including sunitinib, axitinib, pazopanib, sorafenib, cabozantinib, bevacizumab in combination with interferon-α, temsirolimus, everolimus and lenvatinib in combination with everolimus. The median overall survival in mRCC patients in clinical trials has increased beyond two years.[23] Despite the improved prognosis with first- and second-line therapies complete and durable responses are rare and drug resistance will eventually develop in the majority of the patients. Second-line treatment has recently been dramatically modified by the report of two phase III trials showing improvement in overall survival and response rate with cabozantinib [24] and the immune checkpoint inhibitor nivolumab [25] over everolimus. Progression-free survival was only improved in the cabozantinib trial. Nivolumab was associated with HRQOL improvement compared with everolimus.[26] Novel immunotherapy strategies including immune checkpoint inhibitors and tumor vaccines need to be further explored. The choice of drugs and the optimal administration sequence have yet to be determined. Given the high cost of these emerging drugs coupled with the cost for management of treatment-related side effects [6,27-29], the development of effective biomarkers that predict treatment response and drug toxicity is urgently needed.[30] ccRCC-approved targeted agents tend to be significantly less effective for non-clear cell RCC.

Moreover, one third of patients with mRCC experience painful bone metastases which lead to the morbidity of skeletal-related events (SREs) including not only bone pain, but also fractures and spinal cord compression requiring radiotherapy or surgery.[31] Data indicate that 85% of RCC patients with bone metastasis experience SREs over the course of their disease with a mean number of 2.4 per patient.[32] The costs associated with hospital visits for SREs

increase which emphasize the need for cost-effective treatment strategies to timely detect, prevent and/or treat SREs.[33] A Danish study showed a shift in costs after implementation of targeted drugs with a decrease of in-patient costs and an increase of out-patient costs compared to cytokine-based immunotherapy.[34] In a recent French study, the increase of hospital costs was mainly driven by in-patient hospitalization and expensive drugs.[35] At best, some patients have extended survival but prognosis is poor once metastases occur with current treatments of advanced RCC, making the costs not justifiable for a struggling health care system which cannot provide universal basic public health and other services.

Two randomized controlled trials are investigating the role and sequence of cytoreductive nephrectomy in combination with targeted therapy. No general guidelines can currently be given on the local treatment of metastases in mRCC patients.[23].

Patient-centered multidisciplinary approach

A patient-centered multidisciplinary approach is critical to decide which treatment options to offer to an individual patient and to minimize both over-treatment of low-risk disease and under-treatment of high-risk disease. This approach may particularly limit the treatment costs of older patients by preventing treatment-related complications, hospitalization, loss of autonomy, and stay in geriatric and rehabilitation units.[36] Multidisciplinary cancer care is often not available in developing countries because of reduced healthcare infrastructure, resources, and skilled healthcare professionals. Multidisciplinary teams, patient advocates and patient organizations play a vital role in clinical trial accrual and trial design, and in the development and implementation of guidelines. One paper reviewed current treatment guidelines for RCC and provided management recommendations that are based on resource availability (financial, skill and logistic resources). Resource levels were defined according to

a four-tier system (basic, limited, enhanced, and maximum), which was previously described by the Breast Health Global Initiative.[20]

Conclusion

Kidney cancer imposes a significant burden on health care systems due to the availability of suitable imaging and biopsy modalities, high cost of treatment that often involves surgery, hospitalization, and regular follow-up. To tackle the growing global burden, we need to develop RCC-specific awareness campaigns such as the World Kidney Cancer Day on June 22, 2017 (http://www.worldkidneycancerday.com/; Figure 1) and prevention strategies, improve diagnosis and treatment, and eliminate disparities in cancer care across the world. More research is required to interrogate the association between potential risk factors and kidney cancer in order to develop prevention strategies and to identify the most appropriate high-risk populations for screening. Awareness and amelioration of known risk factors would be helpful in reducing the risk of developing kidney cancer. Multidisciplinary care, including appropriate imaging, surgery, radiation therapy and medical treatment, are not universally available and drugs with potential for curing advanced kidney cancer are not affordable or available in much of the world. Therefore, we should focus on early detection and curative local therapy. Training of surgeons and physicians, working with kidney cancer patient advocacy organisations, is necessary to manage this disease and, working with patient advocacy organizations focused on kidney cancer, raising awareness among policy makers is needed to increase allocation of resources. A clear understanding of the underlying factors contributing to the increased cost of kidney cancer care is required. Finally, increasing support for research and cost-effective strategies is necessary to provide high quality care and reduce the burden of this disease.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al: Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136:E359-86, 2015
2. Eble JN, Sauter G, Epstein JI, et al: Tumours of the urinary and male genital organs. Lyon, IARC, 2004
3. Mokdad AH, Dwyer-Lindgren L, Fitzmaurice C, et al: Trends and Patterns of Disparities in Cancer Mortality Among US Counties, 1980-2014. JAMA 317:388-406, 2017
4. Sun M, Shariat SF, Cheng C, et al: Prognostic factors and predictive models in renal cell carcinoma: a contemporary review. Eur Urol 60:644-61, 2011
5. Cella D: Beyond traditional outcomes: improving quality of life in patients with renal cell carcinoma. Oncologist 16 Suppl 2:23-31, 2011
6. Shih YC, Chien CR, Xu Y, et al: Economic burden of renal cell carcinoma in the US: Part II--an updated analysis. Pharmacoeconomics 29:331-41, 2011
7. Johnson DC, Vukina J, Smith AB, et al: Preoperatively misclassified, surgically removed benign renal masses: a systematic review of surgical series and United States population level burden estimate. J Urol 193:30-5, 2015

8. Lobo JM, Nelson M, Nandanan N, et al: Comparison of Renal Cell Carcinoma Surveillance Guidelines: Competing Trade-Offs. J Urol 195:1664-70, 2016
9. Znaor A, Lortet-Tieulent J, Laversanne M, et al: International variations and trends in renal cell carcinoma incidence and mortality. Eur Urol 67:519-30, 2015
10. Hunt JD, van der Hel OL, McMillan GP, et al: Renal cell carcinoma in relation to cigarette smoking: meta-analysis of 24 studies. Int J Cancer 114:101-8, 2005
11. Renehan AG, Tyson M, Egger M, et al: Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 371:569-78, 2008
12. Weikert S, Boeing H, Pischon T, et al: Blood pressure and risk of renal cell carcinoma in the European prospective investigation into cancer and nutrition. Am J Epidemiol 167:438-46, 2008
13. Stewart JH, Buccianti G, Agodoa L, et al: Cancers of the kidney and urinary tract in patients on dialysis for end-stage renal disease: analysis of data from the United States, Europe, and Australia and New Zealand. J Am Soc Nephrol 14:197-207, 2003
14. Lotan Y, Karam JA, Shariat SF, et al: Renal-cell carcinoma risk estimates based on participants in the prostate, lung, colorectal, and ovarian cancer screening trial and national lung screening trial. Urol Oncol 34:167 e9-16, 2016
15. Morrissey JJ, Mellnick VM, Luo J, et al: Evaluation of Urine Aquaporin-1 and Perilipin-2 Concentrations as Biomarkers to Screen for Renal Cell Carcinoma: A Prospective Cohort Study. JAMA Oncol 1:204-12, 2015
16. Ljungberg B, Bensalah K, Canfield S, et al: EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol 67:913-24, 2015

17. Farber NJ, Wu Y, Zou L, et al: Challenges in RCC Imaging: Renal Insufficiency, Post-Operative Surveillance, and the Role of Radiomics. Kidney Cancer J 13:84-90, 2015

18. Huang WC, Atoria CL, Bjurlin M, et al: Management of Small Kidney Cancers in the New Millennium: Contemporary Trends and Outcomes in a Population-Based Cohort. JAMA Surg 150:664-72, 2015

19. Tomaszewski JJ, Uzzo RG, Kutikov A, et al: Assessing the burden of complications after surgery for clinically localized kidney cancer by age and comorbidity status. Urology 83:843-9, 2014

20. Chiong E, Tay MH, Tan MH, et al: Management of kidney cancer in Asia: resource-stratified guidelines from the Asian Oncology Summit 2012. Lancet Oncol 13:e482-91, 2012

21. Kowalczyk KJ, Choueiri TK, Hevelone ND, et al: Comparative effectiveness, costs and trends in treatment of small renal masses from 2005 to 2007. BJU Int 112:E273-80, 2013

22. Bekema HJ, MacLennan S, Imamura M, et al: Systematic review of adrenalectomy and lymph node dissection in locally advanced renal cell carcinoma. Eur Urol 64:799-810, 2013

23. Escudier B, Porta C, Schmidinger M, et al: Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 27:v58-v68, 2016

24. Choueiri TK, Escudier B, Powles T, et al: Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol 17:917-27, 2016

25. Motzer RJ, Escudier B, McDermott DF, et al: Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 373:1803-13, 2015

26. Cella D, Grunwald V, Nathan P, et al: Quality of life in patients with advanced renal cell carcinoma given nivolumab versus everolimus in CheckMate 025: a randomised, open-label, phase 3 trial. Lancet Oncol 17:994-1003, 2016

27. Hagiwara M, Borker R, Oster G: Economic burden of adverse events in patients with metastatic renal cell carcinoma. Clin Ther 35:1955-1963 e2, 2013

28. Hagiwara M, Hackshaw MD, Oster G: Economic burden of selected adverse events in patients aged >/=65 years with metastatic renal cell carcinoma. J Med Econ 16:1300-6, 2013

29. Geynisman DM, Hu JC, Liu L, et al: Treatment patterns and costs for metastatic renal cell carcinoma patients with private insurance in the United States. Clin Genitourin Cancer 13:e93-100, 2015

30. Garcia-Roig M, Ortiz N, Lokeshwar V: Molecular marker for predicting treatment response in advanced renal cell carcinoma: does the promise fulfill clinical need? Curr Urol Rep 15:375, 2014

31. Wood SL, Brown JE: Skeletal metastasis in renal cell carcinoma: current and future management options. Cancer Treat Rev 38:284-91, 2012

32. Woodward E, Jagdev S, McParland L, et al: Skeletal complications and survival in renal cancer patients with bone metastases. Bone 48:160-6, 2011

33. Antczak C, Trinh VQ, Sood A, et al: The health care burden of skeletal related events in patients with renal cell carcinoma and bone metastasis. J Urol 191:1678-84, 2014

34. Soerensen AV, Donskov F, Kjellberg J, et al: Health economic changes as a result of implementation of targeted therapy for metastatic renal cell carcinoma: national results from DARENCA study 2. Eur Urol 68:516-22, 2015

35. Maroun R, Maunoury F, Benjamin L, et al: In-Hospital Economic Burden of Metastatic Renal Cell Carcinoma in France in the Era of Targeted Therapies: Analysis of the French National Hospital Database from 2008 to 2013. PLoS One 11:e0162864, 2016

36. Ploussard G, Albrand G, Rozet F, et al: Challenging treatment decision-making in older urologic cancer patients. World J Urol 32:299-308, 2014


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