Colorectal cancer screening in kidney disease patients: working backwards

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Periodic colorectal cancer (CRC) screening in the general population receives one of the highest recommendations from the US Preventative Health Care Services Task Force and many other practice guideline organizations based on consistent strong evidence from clinical trials. However, the evidence is for subjects at average risk with average life expectancies. In this journal, Wong et al. examine the net benefit and cost-effectiveness of CRC screening in dialysis patients not on the wait list, dialysis patients wait-listed for a kidney transplant and kidney transplant recipients. The benefits of screening were estimated to be 2.6 added days of life for each dialysis patient, 6.9 days for wait-listed patients and 12 days for those transplanted. The benefits accruing to kidney transplant patients were much less than their earlier study showing a benefit of 24 days, probably because the model assumed the transplanted graft never failed. Not surprisingly the cost-effectiveness ratios are high in the former two groups but reasonable in the transplanted population. Although there is a lack of direct evidence, these and other modeling studies suggest the benefits of CRC screening in patients with functioning kidney transplants may well be equivalent to the benefit in the general population. Given the potential harm of screening and the short life expectancies of dialysis patients, the benefits of CRC screening will be small and uncertain. Not screening many of our older dialysis patients would be consistent with guideline recommendations that CRC screening only be undertaken in patients with life expectancies >10 years.

Cancer prevention is high on the healthcare wish lists of both provider and patient [1]. However, there is nothing more controversial than screening to prevent cancer. Whether there has been a recent catharsis or simply a swing in the pendulum, many are not happy with the trend that sees guidelines pulling back with reductions in the frequency of screening, recommendations that screening be delayed to older ages or ceased at a certain age and recognition that some patients are currently inappropriately screened [2]. It is ironic that some cancers such as prostate cancer are frequently screened for in men yet the evidence of benefit is weak, whereas participation rates are relatively low for colorectal cancer (CRC) screening where the evidence of benefit is strongest [3].

A great deal of thought and effort is expended in finding the right balance. Nonetheless, cancer interest groups will always argue that any evidence of benefit is reason enough, whereas task forces believe that there must be strong unbiased evidence (randomized trials of screening) that show significant benefits in hard endpoints (lives saved) and that these benefits must significantly outweigh any potential harms of screening. Like all population screening strategies, the benefits are for the few while requiring participation of many. It is also the many that are potentially subjected to the harms. There are the risks of false-positive screens that result in unnecessary psychological distress, intrusion of time and invasive procedures, finding indolent lesions that may never pose a risk to an individual patient (length bias), later risks associated with further invasive testing and treatment or simply finding lesions earlier with no impact on overall outcomes (lead bias). The erosion of length and quality of life from these harms is not always appreciated nor captured. These have only recently been enumerated in detail for breast and prostate cancer screening and the analyses have been sobering. A recent study on prostate cancer shows the net benefits may be eroded completely by diagnosis and treatment complications and their effects on quality of life [4].

Most importantly, the recommendations to screen are for average risk patients with average life expectancies or for screening in higher risk populations. However, there has been an undercurrent that all patients should have the right to screening, not to do so is an error of omission, and quality of care can be measured by examining screening rates [5]. In fact, the USRDS at one time tracked prostate and breast cancer screening in US dialysis patients as a measure of quality care [6]. The issues become complex in subpopulations with reduced life expectancies and even more so if these populations are at increased cancer risk. The chronic kidney disease (CKD) population is very much an example where the recommendations might blur. Most agencies do not recommend CRC screening in patients with life expectancies <5 years, since the benefits of detecting early lesions that become problematic
would take 5 years to see a benefit and these patients are likely to die of something else in the interim from competing risks [7, 8]. In fact, the American College of Physicians suggests limiting screening to those with life expectancies of >10 years [8]. Patients with CKD, and especially those on dialysis, have markedly reduced life expectancies. In the USA, the average life expectancy for all dialysis patients aged 50–54 is 6.4 years and for patients aged 60+ is <5 years [9]. In effect, screening may well be inappropriate for most ESRD patients.

However, there is evidence that colon cancer is increased in CKD populations, particularly in transplanted patients with greater life expectancies [10]. Although years of remaining life are greater in transplanted patients compared with dialysis patients, life expectancies remain about one-third less in transplanted patients compared with the general population [9]. Colon cancer is reported to be ∼1.5- to 2.5-fold higher in the kidney transplant population [10–12]. Here, the balance of increased risk in a population with a shorter life expectancy makes decision-making interesting. In the article by Wong et al. [13] in this journal, the benefits and cost-effectiveness of CRC screening were explored in Australian/New Zealand patients on dialysis, on the wait-list and with a transplant. Not surprisingly, the benefits were low and cost-effective ratios high in the former two groups but reasonable in the transplanted population. In regard to my review, there are some important points in this analysis that deserve comment. First, this is a very detailed and comprehensive analysis consistent with many similar efforts from this group that readers should be aware of including screening for colorectal, kidney, breast and cervical cancer [14–17].

Second, the probabilities are derived from the Australian/New Zealand population and may not exactly translate to other regions. For example, dialysis mortality rates in the USA are generally higher than in other countries, such that the net benefit of CRC screening will be less [18]. In an economic decision analysis model of US patients, periodic CRC screening was predicted to increase life by <1 day in US dialysis patients, 7 days in transplant recipients compared with nearly 20 days in the general population [19]. In this US analysis, the rates of CRC were assumed to be the same in all populations. If a 2.8-fold higher rate of cancer was modeled, then the net benefits of screening were about the same (20 days) in the kidney transplant patient compared with the general population. In an earlier modeling CRC screening study published by Wong et al. [14] in 2009 of AUS/NZ kidney transplant recipients who experienced increased CRC rates, enrollees were predicted to gain 24 days per person screened. Both of these modeling studies in kidney transplant recipients compare favorably with CRC screening studies in the general population that estimate the magnitude of the benefit to be ∼24 days [20].

In comparison, Wong et al. [13] reports in this journal the benefits of screening to be 2.6 days for dialysis patients not on the transplant list, 6.9 days for those on the list and 12 days for those transplanted. The benefits accruing to transplanted patients were much less than their earlier study showing a benefit of 24 days [14]. So why are the two studies so different? Some of the differences are hidden in the analysis. In the earlier quoted study, kidney transplant patients were assumed to always have a functioning transplant [14, 18]. In this recent analysis, patients with failed grafts continue to receive screening with much reduced benefits. Many of the patients on the wait-list will receive a transplant and enjoy a greater life expectancy but at a higher CRC risk. The implication is that the benefit accrues mostly to those with a transplant (better life expectancy and higher CRC risk), not those on dialysis.

Thirdly, they examine average life expectancies in their end-stage renal disease (ESRD) population. I expect that their dialysis population not wait-listed was healthier than my own. In a recent study of incident patients deemed to have contraindications to transplantation from our center, those <age 60 had a median survival of only 3 years (personal communication). As in the general population, there will be a distribution of life expectancies within all subgroups. Although an individual’s future outcomes are hard to predict, I would expect that we as clinicians can predict with some confidence that a kidney transplant recipient without significant comorbidity and excellent graft function on immunosuppression would more likely benefit from CRC screening than a diabetic patient with a failing graft or a dialysis patient not eligible for the wait-list because of active vascular disease. On the other hand, a 50-year patient on home dialysis that refuses to be transplanted with a family history of CRC might benefit.

As discussed as a limitation of Wong et al. [13], there have not been CRC screening trials in ESRD patients to ensure significant margins of benefit especially in individuals with comorbidities. What is also not available is information about whether our estimates of cancer-related deaths in these medical decision analyses models are in fact correct. What we need to know is how many deaths in our CKD population are in fact related to CRC. Sadly, this is the type of information that is critical to inform medical decision-making. If deaths from CRC comprised a significant percentage of all deaths in this population, then by working backwards, decisions about screening would be easier. Additionally, we need to know how these screening tests perform (specificity and sensitivity) in the CKD population. This information is presently being collected prospectively by Wong et al. [21].

There are several areas of uncertainty that are worth mentioning. One is the role of CRC screening in potential transplant recipients. Our center requires screening with fecal occult blood (FOBT) in those over 50 years of age. Those with positive screens require colonoscopy. We have not formally evaluated this strategy. Some could argue, given the frequency of lesions and the potential of immunosuppression to accelerate cancer growth, that all should require colonoscopy. It remains unknown whether screening significantly delays the transplant evaluation and whether the detection of small lesions further delays access to the list. Another area of uncertainty is whether all older ESRD patients would benefit from being screened once (as opposed to periodically). It is not clear whether CKD patients have higher rates of ‘incidental screening’ as investigations are frequently performed to define the cause of anemia in this population (ascertainment bias). A third area of uncertainty is the point when the reduced life expectancy associated with a low GFR renders screening of an average risk CKD pre-dialysis patients of low value.
This also speaks to the general question of screening methodology. There is great enthusiasm to screen with colonoscopy rather than FOBT. The compelling argument is that more lesions are detected by colonoscopy or rather many are missed with FOBT [22]. While this is true, most of the evidence provided by screening studies have been done with FOBT or more recently with flexible sigmoidoscopy [23]. In addition, FOBT is done annually such that the most important lesions will eventually be detected. What is more important is that some form of screening be done in appropriate patients, and to increase participation, different strategies should be considered as complementary rather than competing. At present, several imaging (colonoscopy every 10 years, flexible sigmoidoscopy every 5 years, CT colonography) approaches as well as annual stool FOBT (guaiac or immuno-histochemical), although not necessarily equivalent, should be considered options and tailored to available resources and the patient [8]. Not all patients will agree to colonoscopy, despite the wishes of some providers. Participation rates in general are higher for FOBT than imaging studies [24].

For the many reasons noted above, undertaking CRC screening (and prostate and breast cancer screening) in the CKD population should be individualized and patient-centered. Do they want it and do they understand the risks and benefits [25, 26]? In the end, it is the physicians who must determine the balance and make recommendations with the individual patient. As in the general population, there are distributions of life expectancies at any given age. For example, at the age of 50, there are those with a life expectancy in the top 25% that are predicted to have a 3.8% chance of dying from CRC whereas those in the bottom 25% are predicted to have a 1% chance of dying from CRC [26]. Frail patients on dialysis that are not candidates for a transplant are likely to have life expectancies much less than the bottom 25%, will likely benefit much less from screening but be exposed to the same or even greater harms.

In summary, despite the lack of trials in the CKD population, the screening modeling studies noted above give us reasonable and prudent direction. Transplanted patients with good graft function and life expectancies between the age of 50 and 70 should be encouraged to participate in CRC screening and may well derive the same expected benefits as screening healthy patients in the general population. For all others, this strategy should be carefully considered only in patients with exceptional life expectancies or at even higher risks of CRC. Periodic CRC screening should not be a metric of quality of care in the average ESRD patient and for many may be an indicator of inappropriate care [25, 27].

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Sleep apnoea and the potential benefits of a good night’s sleep in patients receiving maintenance dialysis

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Premature cardiovascular (CV) death remains the leading cause of mortality in patients with endstage renal disease (ESRD). Modification of conventional CV risk factors, such as dyslipidaemia, has only limited impact on CV disease in this population [1, 2], an observation that has prompted the search for novel mechanisms and therapeutic targets. The publication in this issue [3] provides a potential link between sleep apnoea and fluid overload in patients receiving haemodialysis, and identifies a novel, potentially remediable, risk factor for CVD in this population.

Obstructive sleep apnoea (OSA) is a condition characterized by transient episodes of apnoea or hypopnoea due to obstruction of the upper airway during sleep. Sufferers are often awoken from sleep due to paroxysmal asphyxia with prompt resolution of hypoxaemia and hypercapnia on arousal. In the general population, OSA has been associated with adverse CV outcomes and is linked with systemic and pulmonary hypertension, nocturnal cardiac arrhythmias, coronary artery disease, heart failure and cerebrovascular disease [4]. In ESRD patients, a number of studies have implicated OSA with markers of CV disease and poorer survival [5]. Furthermore, OSA is significantly more common in ESRD patients compared with the general population, and the usual risk factors for OSA (such as obesity, craniofacial abnormalities, nasal congestion and smoking) do not usually apply to dialysis patients. Potential mechanisms implicated with higher prevalence of OSA in ESRD patients include the desensitizing effects of uraemia or metabolic acidosis on higher respiratory control centres. These hypotheses originate from observational studies demonstrating improvement in OSA after removal of these biochemical abnormalities by renal transplantation or more intensive dialysis. Furthermore, missing