Chapter 19: Non-Skin Malignancies

19.1: Develop an individualized screening plan for each KTR that takes into account the patient's past medical and family history, tobacco use, competing risks for death, and the performance of the screening methodology. *(Not Graded)*

19.2: Screen for the following cancers as per local guidelines for the general population *(Not Graded)*:

- **Women: cervical, breast and colon cancer;**
- **Men: prostate and colon cancer.**

19.3: Obtain hepatic ultrasound and alpha feto-protein every 12 months in patients with compensated cirrhosis. *(Not Graded)* [See Recommendations 13.5.4 (HCV) and 13.6.5 (HBV).]

HBV, hepatitis B virus; HCV, hepatitis C virus; KTR, kidney transplant recipient.

Background

Screening for cancer has both benefits and harm. In KTRs with multiple comorbidities, it is essential to consider the extent and magnitude of potential harm, so it can be weighed against the risks of disease and benefits of early detection. There is good reason to believe that screening test performance, harm from interventions and the life years to be gained by early intervention may be substantially different in KTRs compared to that in the general population. Hence, careful individual appraisal needs to be exercised when making recommendations for screening of KTRs (643).

In general, the better the individual's prognosis, the higher the risk of disease, and the lower the risk of harm from screening, the greater is the chance of benefit (644). If, on the other hand, the individual has a poor prognosis from cardiac or other comorbidity, the risk of the disease to be screened is not high and the harm from screening is significant, the less it can be justified. For example cervical cancer screening of an unvaccinated 45-year-old patient with a well-functioning kidney allograft and no comorbidities is easier to recommend than fecal occult blood testing (FOBT) and subsequent colonoscopy in a 69-year-old patient with type II diabetes and severe CAD. The likely incidence of disease needs to be taken into account as well as the standardized incidence ratio (SIR) as performed in Table 29, since the two factors taken together define the likely risk of any given disease in an individual KTR. Unfortunately, there are no RCTs on screening for cancer in KTRs.

Rationale

- Comorbidities and competing risks in KTRs may influence the potential benefits and harm from screening for some cancers.
- The decision to screen for cancer should be individualized.

Screening for cervical cancer

- In the general population, there is good evidence that the benefits of screening outweigh harm.
- In KTRs, cervical cancer is more common than in the general population, and screening may therefore be more beneficial.
- In KTRs with quality of life and life expectancy not greatly reduced from that of general population, the benefits of screening may outweigh harm.
- In the general population, there is evidence that the benefits of human papillomavirus (HPV) vaccination outweigh harm.
- In KTRs, although vaccination may be less effective, there is little reason to believe that benefits would not outweigh harm.

Initiation of screening for cervical cancer is recommended for women within 3 years of onset of sexual activity or age 21 (whichever comes first) in order to detect malignant lesions resulting from persistent human papillomavirus (HPV) infection (www.ahrq.gov/clinic/uspstf/uspscerv.htm; last accessed July 17, 2009) (645). Cervical cancer is more common, may develop more rapidly and may be more aggressive in immunosuppressed patients (646,647), suggesting that KTRs should be screened more frequently (648). American and European transplant guidelines recommend annual screening for cervical cancer with pelvic examination and Pap smear (627,633). Use of HPV DNA testing has not achieved widespread acceptance (www.ahrq.gov/clinic/uspstf/uspscerv.htm; last accessed July 17, 2009). Screening for cervical cancer also provides an opportunity to inspect the anal, vaginal and vulvar regions for cancers that are also increased in female KTRs. The cost of cervical cancer screening in KTRs is modeled at US$ 12 000 per life-year saved comparable to the general population (US$ 25 000 to 50 000 per life-year saved) (649).

In the general population, there is strong evidence that the benefits of vaccination outweigh harm, but the longest

duration of follow-up is 52 months at present. HPV vaccination of girls prior to exposure to HPV infection (for the oncogenic strains 16 and 18, which account for approximately 70% of cervical cancers, and for the wart-causing strains 6 and 11) has been adopted in a number of countries (650,651). The vaccine is inactivated and could thus be used both prior to transplantation and in KTRs, but there is no evidence for effectiveness or safety in immunosuppressed patients.

Screening for breast cancer

- In the general population, there is weak evidence that the benefits of screening outweigh harm.
- In KTRs, the incidence of breast cancer is similar to that in the general population.
- In KTRs with quality of life and life expectancy similar to that of general population, the benefits of screening may outweigh harm.

Mammography for women in the general population ages 50–74 decreases breast cancer mortality by 23% (95% CI 13–31%) (652,653). The incidence of breast cancer is very similar in both the general population and in KTRs. There are no RCTs or studies on which to base advice for or against breast cancer screening in KTRs. The two factors that might influence the decision to screen are screening test performance and potential life-years saved from intervention. American and European transplant guidelines recommend screening in KTRs between 50 and 69 years with an option to screen above the age of 40 years (627,633). Test accuracy for mammography varies with the best results in older women, and the worst results in younger women. Consideration should also be given to the potential physical and emotional harm from false-positive and false-negative screening tests. Models of screening for breast cancer in KTRs suggest that it is cost-effective in nondiabetic Caucasians (654).

Screening for prostate cancer

- In the general population, there is little evidence that the benefits of screening outweigh harm.
- In KTRs, the incidence of prostate cancer is similar to that in the general population.
- In KTRs, it is unclear whether the benefits of screening outweigh harm.

Screening for prostate cancer, using prostate-specific antigen (PSA) and/or digital rectal examination, is controversial in the general population. The most recent recommendation from the USPSTF is to avoid screening men 75 years or older (www.ahrq.gov/clinic/uspstf/uspsprca.htm; last accessed July 17, 2009). They also concluded that there was insufficient evidence to assess the balance of benefits and harm for screening men younger than 75 years old (www.ahrq.gov/clinic/uspstf/uspsprca.htm; last accessed July 17, 2009). The incidence of prostate cancer in KTRs is similar to that in the general population, and being one of the commonest cancers in males, there is a high absolute risk (Table 29). However, there are no data on screening test performance, or benefits in KTRs, and there is good reason to believe that the performance of PSA testing may be different in KTRs compared to the general population. No advice is thus given for or against screening for prostate cancer in KTRs, beyond following local recommendations/standards for prostate cancer screening in the general population.

Screening for colorectal cancer

- In the general population, there is good evidence that the benefits of screening outweigh harm for individuals age 50 years and older.
- In KTRs, the incidence of colon cancer is increased compared to the general population, especially among KTRs less than 50 years of age.
- In KTRs, there are reasons to believe that FOBT may be less specific for colon cancer than in the general population, but there is no evidence to believe that colonoscopy is less sensitive or specific.

Studies in the general population have demonstrated that the benefits of screening generally outweigh the harm (655–658). Guidelines for the general population in Australia/New Zealand, the US and in Europe, recommend screening individuals 50 years and older, using annual FOBT and/or colonoscopy (655). The standardized incidence of colorectal cancer is increased in KTRs compared to the general population, and there is good evidence that colon cancer occurs at a younger age in KTRs compared to the general population (Table 29). American and European transplantation guidelines recommend screening either at age 50 years, or at the age at which it is recommended in the general population in each country (627,633).

Screening with FOBT may be less specific in KTRs, given that the incidence of positive tests from CMV infection and drug toxicities may be high. The harms of colonoscopy must be carefully considered in each individual based upon their comorbidities, since the consequences of the potential complications of colonoscopy are influenced negatively by immunosuppression. In the absence of data on the benefits and harm of screening of KTRs for colon cancer, it is suggested that screening should be performed as currently recommended for the general population with careful individual risk–benefit analysis based upon overall prognosis and comorbidities. A recent analysis suggests that the benefits may outweigh the harm from screening of KTRs aged 35–50 years (659).

Screening for hepatocellular cancer

- In KTRs, the risk of hepatocellular carcinoma is higher than in the general population.
- In the general population, there is no evidence that the benefits of screening outweigh harm.

There are screening recommendations in high-risk groups (patients with cirrhosis and those who are hepatitis B carriers) that include abdominal ultrasound and alpha-feto protein testing every 6–12 months (660–662). Testing every 6 months is based on the estimated doubling time of this tumor (660). The Work Group chose a 12-month testing interval, given uncertainties of the benefits and harm of testing. Both tests have limited specificity and sensitivity (663). Nonetheless screening by gastroenterologists in high-risk patients is reported to be about 50% by questionnaire survey in the United States (664,665), the interventions have significant risks and no RCTs have demonstrated survival benefits. There have been several cost-effectiveness studies but the conclusions have varied widely from very cost-effective to values exceeding US$ 250 000 per quality-adjusted life-year (666). The US National Cancer Institute does not recommend screening (www.cancer.gov/cancertopics/pdq/screening/hepatocellular/healthprofessional/page2; last accessed July 17, 2009) largely because of a concern of uncommon but significant harm due to invasive testing after false-positive screening. There have been two large population-based RCTs in Asia in HBV-infected subjects. The larger study showed some benefit, but was of poor quality, and the second showed no benefit (667,668).

The highest-risk group of KTRs with otherwise good prognosis are those with compensated cirrhosis and chronic viral hepatitis, especially HBV (669). Given that the benefits are inconclusive in high-risk nontransplant patients, the recommendation of the US National Cancer Institute is not likely to differ in KTRs.

Screening for renal cell cancer

- In KTRs, the incidence of renal cell carcinoma is much higher than in the general population; however, there is no evidence that the benefits of screening outweigh harm.

Screening is not generally recommended in the general population. Both relative and absolute risks of renal cell cancer are substantially increased in KTRs compared to the general population. Although there is no good evidence that mortality is reduced, several United States, European and Asian centers are screening for renal cell carcinoma after transplant (670–672). The rate of renal cell carcinoma (number per years of follow-up) is difficult to determine from these reports, but appears to vary considerably. Two important risk factors for renal cell carcinoma in these reports were prior renal cell carcinoma and the presence of acquired cystic disease. A medical decision analysis conducted several years ago, predominantly in dialysis patients with low expected survival rates, determined that the benefits of routine screening would be low (673). Screening will likely detect many unimportant lesions that will require further investigation, treatment and thus possible harm. Nonetheless, significant benefits could accrue to higher-risk transplant recipients with better-than-average life expectancy. Patients with prior renal cell cancer are at risk of both recurrence and new primaries, irrespective of whether they have been transplanted. Some diseases, such as analgesic nephropathy, tuberous sclerosis and acquired cystic disease are associated with an increased risk of renal cell carcinoma. The American Society of Transplantation guidelines found no evidence to advise screening with either imaging or urine cytology (627).

Research Recommendations

- Observational studies are needed to better define age-specific SIR for most cancers, with preliminary analyses suggesting that younger KTRs have a greatly increased SIR compared to older KTRs.
- Studies on the performance of FOBT in KTRs would help determine its potential role for screening KTRs.
- A RCT should be performed to assess the benefits and harm of screening vs. no screening for renal cell carcinoma. Preliminary data are needed to define mortality rates from renal cell carcinoma after transplantation, and determine age-specific SIR, since analyses suggest that younger KTRs have a greatly increased SIR in comparison to older KTRs.