BC CANCER

Provincial Health Services Authority

# Journal of Family Practice Oncology

Issue Number 35, Fall 2020 | www.fpon.ca

## BEST PRACTICE CANCER CARE GEMS *IN THIS ISSUE*



# How to recognize skin cancers that don't obviously look like skin cancer

*by Dr. Harvey Lui, Dermatologist, BC Cancer and Department of Dermatology and Skin Science, University of British Columbia, and Dr. Sunil Kalia, Dermatologist, and Associate Professor, Department of Dermatology and Skin Science, UBC*

During medical school, all physicians learn that there are 3 main forms of skin cancer by committing their visual memories to the classic clinical features of each of these conditions *(Table 1)*. Although accurate and timely visual recognition of these features followed by confirmatory skin biopsy will diagnose a significant majority of skin cancers, there are many instances where cutaneous neoplasms are missed, particularly for the superficial or *in situ* variants of each of these tumours.

***Superficial skin cancers*** (Table 2) are often missed because physicians may not be as familiar with their clinical features as they are with the more classic presentations. In general, superficial skin cancers:

- are usually asymptomatic and therefore do not arouse as much alarm or concern for patients and their physicians;
- do not present as "tumours", i.e. lumps or bumps within the skin;
- evolve very slowly and insidiously; many superficial skin cancers may be present on the skin for many years before being recognized or investigated; and
- grow by lateral extension rather than via vertical dermal invasion.

*continued on page 2*

Dr. Harvey Lui is a dermatologist on staff at BC Cancer and Vancouver General Hospital, and a highly regarded educator with the Family Practice Oncology Network.

Dr. Sunil Kalia is a dermatologist, and part of BC Cancer's Skin Tumour Group and BC Cancer Research's Cancer Control Group.

Dr. Francis Zih is a surgical oncologist at Surrey Memorial Hospital.

# Don't miss our virtual fall conference: November 13, 2020 on skin cancer

Registration is now open at fpon.ca for the Family Practice Oncology Network's first-ever virtual conference, *Skin Cancer: Interactive Scenarios & Practical Approaches for Primary Care*. The event will run from 1-4 p.m., November 13, 2020 featuring, a 100% case-based format targeted directly to primary care needs.

The afternoon includes a two-part focus covering both a dermatological approach to preventing, diagnosing and managing common skin cancers, and a surgical approach to staging and managing melanoma from a primary care perspective. Expert dermatologists, Drs. Harvey Lui and Sunil Kalia, will lead the dermatology portion of the conference, and leading surgical oncologist, Dr. Francis Zih, will present on melanoma and guide ensuing discussion. The event includes a strong interactive component with ample opportunity to engage with the speakers and maximize learning to enhance the cancer care you provide.

Register today at www.fpon.ca
2.75 Mainpro+ credits
Cost: $50 all disciplines

For full details visit www.fpon.ca or contact Dilraj Mahil at dilraj.mahil@bccancer.bc.ca

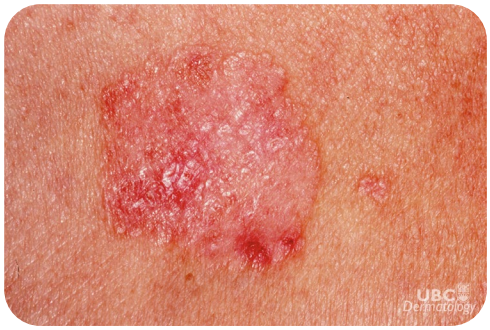



Figure 1a – superficial basal cell carcinoma

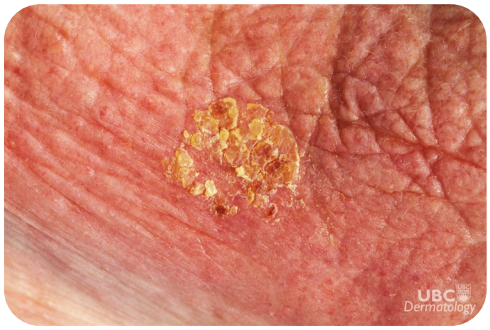



Figure 1b – squamous cell carcinoma in situ

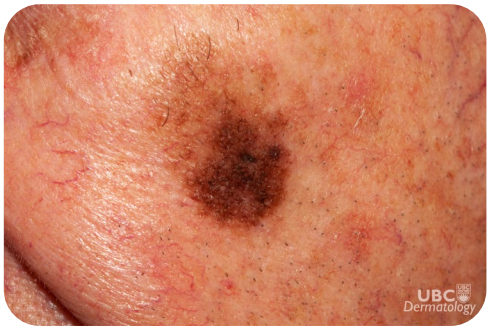



Figure 1c – lentigo maligna

*How to recognize skin cancers continued from page 1*

Perhaps the biggest challenge in diagnosing superficial skin cancers is that they can easily mimic benign skin disorders including psoriasis, eczema, tinea fungal infection, solar lentigines, and seborrheic keratosis. By the time a superficial skin cancer is diagnosed (e.g. figures 1 a, b, & c), the lesion will often have had a history of being unsuccessfully treated with topical steroids, antifungal agents, topical antibiotics, and/or attempted liquid nitrogen cryotherapy.

The usual treatment of choice for superficial skin cancer is surgery. In selected cases, topical therapy with imiquimod or fluorouracil, curettage and electrosurgery, cryotherapy, or radiation therapy can be used. Although the overall prognosis for superficial skin cancer is good to excellent, delays in diagnosis can result in the lesion becoming relatively large, thus requiring more extensive surgery which in turn results in greater disfigurement and patient morbidity. It is also possible that the lesions can become invasive and then have a poorer prognosis.

*Contact Dr. Harvey Lui at harvey.lui@ubc.ca and Dr. Sunil Kalia at sunil.kalia@ubc.ca*

## Table 1: Classic visual features of skin cancer

| | |
|---|---|
| Basal cell carcinoma (BCC) | • eroded or ulcerated nodule or papule<br>• translucent pearly appearance with rolled edges that become more apparent when the skin is stretched<br>• telangiectasia |
| Squamous cell carcinoma (SCC) | • solid nodule or papule<br>• firm and indurated<br>• thick, irregular adherent scale |
| Melanoma | • "*ABCDE*" rule, i.e. *A*symmetry, *B*order irregularity, *C*olour variegation, *D*iameter > 6 mm, *E*volution or *E*ccentricity |

## Table 2: Superficial variants of skin cancer

| Tumour category | Superficial variant | Key features |
|---|---|---|
| BCC | Superficial BCC (Figure 1a) | • thin plaque or papule that is often red, scaly, and mistaken for an inflammatory dermatosis<br>• usually well-circumscribed |
| SCC | SCC *in situ*, also known as Bowen disease (Figure 1b) | • may often occur on the trunk or extremities instead of the face<br>• in the case of superficial BCC, look for a subtle, thin, thread-like rolled pearly border along the margins (more apparent when the skin is stretched) |
| Melanoma | Lentigo maligna, an *in situ* variant of melanoma (Figure 1c) | • usually occurs on the head and neck region within areas of extensive sun damage (i.e. photoaging)<br>• flat patches or macules with significant colour variegation<br>• usually larger than most solar lentigines |

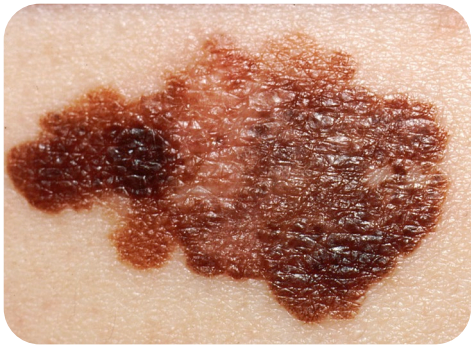
### Clinical Pearls for Diagnosing Superficial Skin Cancer

- Become familiar with the unique and characteristic features of superficial skin cancers;
- Maintain a high index of suspicion for superficial skin cancer and recognize that these lesions are very common;
- If a lesion that initially looks like it is primarily inflammatory in appearance, but doesn't respond to topical therapy, reconsider your diagnosis, especially if the lesion is solitary; and
- If in doubt, it's usually easy to biopsy the lesion in question; for suspected lentigo maligna of the face, multiple small biopsies or one broader superficial "shave-type" biopsy might be acceptable.

# Melanoma insight for primary care

*By Dr. Francis Zih, Surgical Oncologist, Surrey Memorial Hospital*

Melanoma is the 7th most commonly diagnosed cancer in Canada. In 2020, approximately 8,000 Canadians will be diagnosed with melanoma, and about 1,300 will die from melanoma. Risk factors include UV radiation exposure, skin type, personal or family history of melanoma, and a history of atypical nevi or moles. The majority of patients will initially present with localized disease. Prognosis for early stage melanoma is excellent. Patients with a primary tumour



thickness of 1mm or less (T1), with no other adverse features, have a 5-year survival of over 90%. If there is local regional nodal spread, the 5-year median survival in stage III patients is about 65%. Patients with stage IV metastatic disease have a 5-year survival approaching 25%.

Patients presenting with a suspicious pigmented lesion should undergo a thorough skin examination and all draining nodal basins should be evaluated. For the primary tumour, T-stage is defined by tumour thickness. Shave biopsy may underestimate the full depth of the tumour and is discouraged. Preferred modalities include punch or excisional biopsy. A potential disadvantage for upfront excisional biopsy is margin status. There are well-defined guidelines for excision margin based on tumour thickness. For example, any primary tumour over 2mm in depth requires a 2cm margin. The 2cm margin will be measured from the scar of the excisional biopsy. At certain sites of the body, this may result in the need for a skin graft. A full -thickness punch biopsy can provide accurate T staging without potentially compromising local therapy.

Clinically node-negative patients with a primary tumour over 1mm should be offered sentinel lymph node biopsy (SLNB) to complete staging and to help guide adjuvant therapy. Thin melanomas (<1mm), in general, have a low risk of a positive sentinel node (<5%). However, if there are adverse pathologic features like ulceration or high mitotic rate, then an SLNB should be discussed and offered. Sentinel node biopsy typically includes the use of preoperative lymphoscintigraphy as well as intraoperative subdermal injection of isosulfan or methylene blue dye to help identify the node(s). On average, 2-3 nodes are excised during SLNB. The morbidity of SLNB is low, and lymphedema rate is less than 5%.

In 2017, the landmark Multicenter Selective Lymphadenectomy Trial (MSLT-II) demonstrated no survival benefit after immediate completion of lymph node dissection in patients with a positive sentinel node. In general, patients with node-positive disease will be offered close nodal surveillance with ultrasound as well as adjuvant therapy. Stage III and IV melanoma patients are eligible for systemic therapy, namely either BRAF-targeted therapy or immune checkpoint inhibitors.

Don't miss Dr. Francis Zih's case-based presentation at our Nov 13 Virtual Fall Conference: Skin Cancer – Interactive Scenarios & Practical Approaches for Primary Care. Register at www.fpon.ca

Patients with resected early stage melanoma (Stage I and II) should undergo active surveillance with examination every 6 months for 5 years. Examination should include a complete skin exam looking for new lesions, local recurrence, and in-transit disease. All nodal basins should also be evaluated. Routine imaging is not necessary. Stage III patients with a positive sentinel node should undergo regular ultrasound surveillance of the involved nodal basins. Additional cross-sectional imaging may be indicated in the presence of new symptoms.

*Contact Dr. Francis Zih at francis.zih@fraserhealth.ca*

# New video on benefits of quitting smoking after a cancer diagnosis

BC Cancer's Smoking Cessation Program proudly presents *Quitting Smoking After a Cancer Diagnosis* – a 2 minute video with patient partners, Bill and Anita Callahan, and Project Lead, Dr. Renelle Myers, exploring the journey of quitting smoking, and the benefits of quitting after a cancer diagnosis: www.youtube.com/watch?v=GH9tzvS6Ekk

*"Dr. Myers advised me before my bronchoscopy that stopping smoking prior to surgery would benefit my recovery and my fight against cancer. I could not ignore this advice and, with the support of my patient and understanding wife, I was able to quit smoking immediately after the bronchoscopy. For me, quitting smoking for any length of time had been impossible until I was told I had cancer in my lung."*
– Patient Partner Bill Callahan.

*continued on page 4*

# Fertility after cancer care

*By Dr. Beth Taylor MD, FRCSC, Gynecologic Reproductive Endocrinology & Infertility, Olive Fertility Centre, Vancouver, BC*

Reproductive-aged men and women are surviving cancer and its treatment more than ever. Five-year survival rates for testicular cancer, hematologic malignancies, breast cancer, and others may be 90% or greater. However, achieving such high survival rates often comes with a cost to the survivor's fertility, an important part of quality of life.[1]

View the full webcast on this topic at www.fpon.ca – Continuing Medical Education.

Treatments like chemotherapy, radiation and surgery can all impact the quantity and quality of sperm and eggs. Pelvic radiation and surgery for gynecologic cancers can harm the uterus.

How can we help our cancer patients preserve their fertility?

## Males

The most common strategy to preserve fertility is cryopreservation (freezing) of sperm before treatment for later use. Ideally, sperm is ejaculated, washed and then frozen. In some instances, testicular sperm aspiration may be appropriate. Cryopreservation of testicular tissue from prepubescent males is promising, but not currently available in British Columbia.

Frozen ejaculated sperm can be used for intrauterine insemination or In Vitro Fertilization (IVF) in the future, while sperm extracted from the testes or frozen as tissue necessitates the use of IVF.

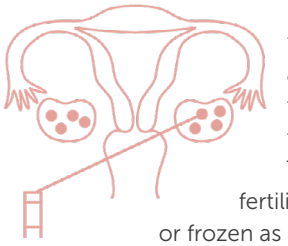
## Females

Preservation of female fertility is more complex than in males.

Suppression of ovarian function with an oral contraceptive pill or a GnRH Agonist (e.g. Lupron) may "shield" the ovaries from the gonadotoxic effect of some chemotherapies, particularly in women with breast cancer.[2]

Conservative fertility-sparing treatment such as ovarian transposition, radical trachelectomy in cervical cancer, hormonal treatment of early endometrial cancer, and conservative surgical management of early-stage epithelial ovarian cancer may be possible for certain women with early invasive disease. However, the majority of women with genital tract malignancies will require more aggressive and fertility limiting treatment.

Cryopreservation of eggs or embryos is a viable option for those facing gonadotoxic therapy. In this technique, the ovaries are stimulated with follicle stimulating hormone



(FSH) injections for 8-12 days, and eggs are then extracted transvaginally. They can be fertilized with sperm or frozen as unfertilized eggs. Depending on the woman's age and ovarian reserve, success rates are as high as 70%. Cost and time are often limiting factors: the cost is $8,000 to $10,000, and many women do not wish to delay cancer treatment.

For those who are unable to preserve their fertility, parenthood can still be achieved through the use of donor sperm, donor eggs, surrogacy and adoption.

Discussing fertility preservation is an important part of modern oncology care.

*Contact: Dr. Beth Taylor at btaylor@olivefertilty.com*

## References

1. Barr RD, Ferrari A, Ries L, Whelan J, Bleyer WA. Cancer in Adolescents and Young Adults: A Narrative Review of the Current Status and a View of the Future. *JAMA Pediatr*. 2016;170(5):495-501.
2. Findeklee S, Radosa JC, Takacs Z, et al. Fertility preservation in female cancer patients: current knowledge and future perspectives. *Minerva Ginecol*. 2019;71(4):298-305.

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*New video on benefits of quitting smoking continued from page 3*

Smoking cessation is considered first line therapy for cancer patients. Stopping smoking at the time of a cancer diagnosis can improve a patient's treatment response and reduce side-effects. Empowering patients who are smokers with education – advising them to stop smoking at the time of a cancer diagnosis – is one of the **most important** parts of their treatment. People live longer and live better if they stop smoking at the time of their treatment. Evidence shows as well that patients are most successful when supported by health care professionals in their attempt to quit, and when the approach includes both counselling and pharmacotherapy.

Dr. Myers is the leader and visionary for **BC Cancer's Smoking Cessation Program** launched in September 2019 as part of a national initiative to provide smoking cessation to cancer patients. At BC Cancer, this program is now part of every patient's initial visit designed to screen all new cancer patients for tobacco use, to educate them on the benefits of quitting smoking, and to provide them with tools to quit. The latter includes referral to Quit Now (www.quitnow.ca) delivered by the BC Lung Association on behalf of the Government of BC.

Our hope is that Bill's story will inspire patients to quit smoking when faced with a cancer diagnosis. The more they can be supported, the better chance they will have of successfully quitting smoking, and of responding better to cancer treatment.

Smoking cessation is especially important during the COVID- 19 pandemic as evidence suggests outcomes are worse for patients who smoke and who are going through cancer treatment (www.bccancer.bc.ca/health-professionals-site/Documents/COVID-19%20smoking%20and%20cancer.pdf)

**Smoking Cessation Program**

For health care professionals: www.bccancer.bc.ca/health-professionals/clinical-resources/smoking-cessation-program

For patients/public: www.bccancer.bc.ca/health-info/prevention/tobacco

# Teamwork @ the heart of Comox cancer care

Cancer patients in the Comox Valley on Vancouver Island are fortunate to have a dedicated team of five General Practitioners in Oncology (GPOs) leading local cancer care in partnership with BC Cancer oncologists. Four juggle the demands of family practices working one/two days as a GPO at the North Island Hospital Comox Valley Community Oncology Clinic, while the other brings the focus of an experienced hospitalist to high acuity care. In sharing perspectives on their GPO roles, all remarked on the teamwork that drives their efforts, and the positive impact on patient care.

Team Comox (left to right): GPOs Drs. Amitabh Bakshi, Wai Ling Dan, Tsveta Nikova, and Madelein Smit. Missing, Dr. Aléjandra Farias Godoy.

**Dr. Wai Ling Dan, GPO since 2015:** As a long-time practitioner of hospital medicine, I am impressed by the cooperation and dedication our team brings to cancer care. Our lab, for example, processes needed blood work right away while imaging is completed promptly, and admissions handled immediately if required. Our Emergency Department sees our patients quickly, too, should the need arise, while our nurses and pharmacists go the extra distance every day to ensure chemotherapy is delivered in a safe and timely manner.

I especially like the medical challenge of GPO work, the pace at which care proceeds, and getting to know patients well. There are times of sadness and reflection when someone is doing poorly, but there is much laughter in our days, too, and the work is fulfilling. More GPOs are needed though, as we strive to meet increasing demands and risk losing resilience.

We've built a beautiful team here, and the patients are amazing.

*Contact Dr. Wai Ling Dan at the North Island Hospital Comox Valley Community Oncology Clinic.*

**Dr. Amitabh Bakshi, GPO since 2014:** Teamwork is the backbone of our ability to coordinate cancer care locally. My role involves maintaining a good rapport and communication with patients, helping them through a tough time, and enabling them to complete treatment. GPOs serve as a link between specialists and family physicians, advancing care while helping patients understand their disease and treatment. Our patients are grateful to receive treatment locally, and both they and their families appreciate the education and insight provided by the team here, especially by our nurses.

The GPO Education Program is well organized and provides a broad overview of how the system works. It was helpful to meet experts and colleagues from different parts of the province – all adding to a sense of team.

*Contact Dr. Amitabh Bakshi at abakshi07@gmail.com*

**Dr. Tsveta Nikova, GPO since 2018:** I enjoy the balance that GPO work adds to my family practice, and have always been interested in oncology as a fast-evolving field of medicine. Fortunately, new lines of therapy are available, and it is rewarding to see our patients enjoy a good quality of life.

As GPOs, we step into a person's life when he/she is vulnerable, and I cherish moments we can meaningfully support their treatment journey. Building a relationship with each patient, understanding their goals, and seeing them regularly, enable us to provide a high level of care.

The GPO Education Program was priceless in terms of the knowledge and experience gained. I feel lucky and privileged to be part of a great GPO team.

*Contact Dr. Tsveta Nikova at tsveta.nikova@gmail.com*

**Dr. Madelein Smit, GPO since 2019:** The opportunity to play a vital role in a person's cancer journey is a privilege, and I continue to build my knowledge. I appreciate, too, that the GPO role is not as rushed as that of a family physician, and find the medical challenge good for the brain!

The GPO Education Program provided excellent foundational knowledge in oncology, and the rotations with BC Cancer – Victoria oncologists prepared me well for the responsibilities involved. All the GPOs here feel well supported by BC Cancer and appreciate their quick replies to our queries. We, in turn, keep patients' family physicians informed of their patients' care and troubleshoot along the way.

There is a growing need, however, for GPO expertise as referrals are increasing weekly. The continuing education that the Family Practice Oncology Network provides helps keep us current.

*Contact Dr. Madelein Smit at maria.smith@viha.ca*

**Dr. Aléjandra Farias Godoy, GPO since 2018:** Dr. Farias Godoy is another valued member of the Comox GPO team who provides additional GPO expertise to Campbell River as needed, maintains a family practice, and serves on the local palliative care team.

## Next GPO Education course begins February 1, 2021

The GPO Education Program includes a two-week didactic Introductory Module held twice yearly followed by 30 days of flexibly scheduled clinical rotation. Full details at www.fpon.ca

# Corridor Consult – Breast Screening Q&A

1. What are the current BC breast screening recommendations?

| AGE | RISK | SCREENING RECOMMENDATION | SELF-REFERRAL |
|---|---|---|---|
| 40-49<br>no family history | Average | Available every two years.<br>Talk to your doctor about when to start screening. | Yes.<br>But provider discussion is recommended. |
| 50-74<br>no family history | Average | Recommended every two years. | Yes. |
| 75+ | Average | Available every two to three years.<br>Talk to your doctor about when to stop screening. | Yes.<br>But provider discussion is recommended. |
| 40-74<br>1st degree relative with breast cancer | Higher than average | Recommended every year. | Yes. |
| 30-74 | High | Recommended every year.<br>Consider if you are:<br>• BRCA 1 or BRCA 2 carrier;<br>• Untestesd 1st degree relative of BRCA 1 or BRCA 2 carrier;<br>• Have a very strong family history of breast cancer;<br>  ◦ 2 cases of breast cancer in close female relatives on the same side of the family, both diagnosed before age 50;<br>  ◦ 3 or more cases of breast cancer in close female relatives on the same side of the family, with at least one diagnosed before age 50.<br>• Chest radiation treatment during childhood. | No.<br>Provider referral is required for initial screen for those 30-39 years old. |

2. Can women without a primary care provider access BC's breast screening program?

A primary care provider (e.g. physician, nurse practitioner) is required to book a screening mammogram, to receive screening results and arrange follow-up procedures.

View the full webcast on this topic at www.fpon.ca – Continuing Medical Education.

3. When is a diagnostic mammogram, as opposed to a screening mammogram, indicated, and how do the two tests differ?

Diagnostic mammography is indicated for individuals with breast symptoms (e.g. palpable lump, nipple discharge), those with breast implants, and those with a personal history of breast cancer. It may also be considered for those not included in the screening recommendations above. The screening program recommends that individuals discuss breast concerns with their primary care provider. If diagnostic mammography is deemed appropriate, then an imaging requisition is required, and the exam is performed at a diagnostic imaging facility. Screening mammography is indicated for asymptomatic individuals, and is available at screening centres based on the above recommendations. Self-referral is generally permitted, except for those at high risk (e.g. BRCA gene mutation) and under the age of 40.

More information related to diagnostic imaging: https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/breast-cancer-and-disease-diagnosis

4. How are women with breast implants screened?

Individuals with breast implants are screened through a diagnostic imaging service. This requires an imaging requisition from their health care provider. The reason for provision through diagnostic rather than screening services is the inclusion of specialized mammographic views requiring additional time and expertise.

5. Is there a role for MRI in breast screening?

Although routine screening with breast MRI of women at average risk is not recommended, exceptions apply for high risk groups. The following groups are recommended for routine breast MRI:

- BRCA1 and/or BRCA2 carriers;
- First degree family relatives of BRCA1 and/or BRCA2 not tested; and
- Chest radiation treatment during childhood.

More information related to diagnostic imaging: https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/breast-cancer-and-disease-diagnosis

6. We know that risk is higher than average for patients with a first degree relative with a history of breast cancer. Does the age of the relative at diagnosis affect screening recommendations?

The screening program suggests that

*continued on page 7*

# Change is upon us, and opportunties present

*By Dr. Cathy Clelland, Program Medical Director, Primary Care*

As I look out my window, I see the change of season is upon us. In healthcare, however, we are coming through the most unpredictable and unprecedented of times. The COVID-19 pandemic saw a shutdown of "elective" care to help flatten the curve and avoid overwhelming our acute care system. Efforts were made to ensure hospitals and emergency services would be able to care for patients in as safe a way as possible. One of the unanticipated consequences, however, was the impact on community primary care. After years of barriers to widespread implementation of virtual care in BC, we saw family physicians shift rapidly to provide most care through virtual means. The need to provide in-person, hands-on services for conditions not appropriate for virtual care, however, was hampered by a lack of PPE.

Dr. Cathy Clelland

Many Divisions of Family Practice worked rapidly to develop strategies to address their communities' need for in-person care optimizing access to PPE – often in a centralized location – to supplement virtual care. As community practices reopen to provide more in-person care, many will continue to embrace virtual care as a means of expanding access. The commitment of community providers to support patients shows that the broader healthcare system needs a strong primary care base to function across the continuum. I thank my community colleagues, and all health care providers, for their efforts to keep us all healthy and safe these past months.

The cancer care system can learn, too, from this experience especially regarding the need for enhanced connectivity (both virtual and in-person). A community approach to cancer prevention and screening, plus strong linkages between community and tertiary care have never been more important. A strong, well supported primary care community is critical for sustainability, for timely access to care, and follow-up. To paraphrase Dr. Bonnie Henry, we are in this together, and together we can improve the experience of our patients and their families through their cancer care journey.

*Contact Dr. Cathy Clelland at cathy.clelland@bccancer.bc.ca*

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*Corridor Consult – Breast Screening Q&A continued from page 6*

a complete family history be obtained when assessing an individual's breast cancer risk. Some patients may then be eligible for referral to the BC Cancer Hereditary Cancer Program (www.bccancer.bc.ca/our-services/services/hereditary-cancer). If a first degree relative (e.g. sister) is diagnosed (with no high risk factors), then the recommendation is to begin screening within the Breast Screening Program at age 40. If the relative was diagnosed under the age of 50, then an individualized consideration of the other relevant risk factors, along with costs and benefits of screening, should be factored into the decision to refer to diagnostic imaging for screening.

7. What is the recommendation regarding routine breast self-exams and routine clinical breast exams by family physicians?

### Breast self-exams

Routine breast self-examinations (when used as the only method to screen for breast cancer) are not recommended for asymptomatic women at average risk of developing breast cancer. Women are encouraged to be familiar with their breast texture and appearance and raise any concerns with their health care provider.

### Clinical breast exams

There is insufficient evidence to either support or refute routine clinical breast exams (in the absence of symptoms) alone or in conjunction with mammography. The patient and health care provider should discuss the benefits and limitations of this procedure to determine what is best for the patient. This excludes women with a prior breast cancer history.

More information: bccancer.bc.ca/screening

## BC Cancer screening resumption update

### Colon Screening Update

Fecal immunochemical testing (FIT), part of the early screening process for colon cancer, has now resumed in BC after the distribution of FIT kits was temporarily suspended in March 2020 due to COVID-19.

Individuals eligible for a FIT test can pick up a kit at any public or private lab across the province with a referral from their health care provider. Individuals, who had picked up a FIT kit prior to screening suspension and have yet to complete it, can now complete and return their kit to the lab.

### Breast Screening Update

Breast Screening centres across the province are now re-booking previously cancelled appointments for June and beyond. Screening reminders are also being sent to those who were due for screening at the time of suspension ahead of those who are coming due. Patients are encouraged to wait to receive their reminder letter before calling to book their screening mammography appointment. The Mobile Mammography Service is now resuming operation, but at a modified schedule to protect both staff and patients. Patients are encouraged to visit the clinic locator at screeningbc.ca to determine when the mobile unit is visiting their community.

The BC Cancer Breast Screening Program is committed to the safety of both patients and staff, and has introduced measures to promote safe cancer screening.

# It begins with you: the BRCA genes in the Ashkenazi Jewish population

*By Allison Mindlin, Genetic Counsellor, BC Cancer Hereditary Cancer Program and Dr. Rona Cheifetz, Medical Lead, Hereditary High Risk Clinic, BC Cancer*

He was your typical patient: Caucasian, male newly diagnosed with metastatic prostate cancer at 72. "How did this happen?" he asks. You explain that cancer is common and usually sporadic. You refer him for treatment, but wait, did you ask about his ancestry? Did you consider that he might be predisposed to cancer?

Allison Mindlin

Dr. Rona Cheifetz

Hereditary Breast and Ovarian Cancer Syndrome, caused by mutations in the BRCA1 and BRCA2 genes, is an uncommon occurrence, with an estimated prevalence of 1 in 400 to 500 in the general population. But for individuals of Eastern European (or Ashkenazi) Jewish background, there is a significantly higher rate of these mutations, with 1 in 40 individuals being a carrier of a BRCA mutation. For those with a significant family history of breast, ovarian, prostate or pancreatic cancer, the likelihood of being a carrier is even greater.

Why does it matter? In short: prevention. The risks of cancer are substantial. Women who have inherited a BRCA1 mutation have a cumulative lifetime risk of 72% of developing breast cancer, and a 44% risk of developing ovarian cancer, while women with a BRCA2 mutation have risk profiles of 69% and 17%, respectively[1]. For men, the lifetime risks of prostate cancer and breast cancer are substantially elevated, while both genders may face an increased risk of pancreatic cancer and melanoma.

Identifying a mutation in women means access to screening breast MRI from age 25 and consideration of prophylactic mastectomies with a strong recommendation for prophylactic salpingo-oophoretomy between ages 35 and 45. For men, increased screening from a younger age is recommended for male breast and prostate cancer. Increasingly, genetic status is playing a role in targeted therapeutics. For BRCA mutations, this may mean improved access and better survival using drugs called PARP-inhibitors.

Children of a mutation carrier have a 50% risk of carrying a mutation; therefore, identifying a carrier has a ripple effect within a family. It allows for risk stratification of relatives and access to targeted screening and prophylactic surgeries for those at high risk of cancer.

## Reference


1. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers Karoline B. Kuchenbaecker et al. JAMA. 2017;317(23):2402-2416


**As a family physician, the first step begins with you.**

Ascertaining a basic family history and ancestry for your patients is key. The Hereditary Cancer Program at BC Cancer is a provincial program that offers genetic assessment and funded genetic testing to patients in BC and the Yukon. Individuals of Ashkenazi Jewish descent (even those with 1/8 AJ ancestry) with ANY family history of breast, ovarian, prostate or pancreatic cancer are eligible for a genetic counselling appointment and testing for the BRCA1 and BRCA2 mutations. Even individuals without cancer are eligible for directed genetic testing. For more information and to access a referral form, please visit: http://www.bccancer.bc.ca/our-services/services/hereditary-cancer or call (604) 877-6000 local 672198. For additional information about the BRCA genes, their impact on the Jewish population, and information on public and private testing options in BC and educational events, please visit: BRCAinBC.ca

# Hereditary cancer program updates

*By Mary McCullum, Nurse Educator, and Jennifer Nuk, Clinical Coordinator/Genetic Counsellor, BC Cancer Hereditary Cancer Program*

## Storing a blood sample

The most informative genetic testing for a family usually starts with testing a sample from an affected "index." If that person's health status is poor or might decline suddenly, please consider storing a blood sample for their family's benefit. The Hereditary Cancer Program recently revised its Urgent DNA Storage paperwork to make this process as clear and simple as possible. The new package includes an instruction page, requisition and information page for the patient/family, and is available at www.bccancer.bc.ca/health-professionals/clinical-resources/hereditary-cancer.

*continued on page 9*

# HPV vaccination in BC: where are we now?

*By Laurie Smith, Research Program Manager, HPV Related Diseases, Dr. Marette Lee, Gynecologic Oncologist, BC Cancer – Vancouver, and Dr. Gina Ogilvie, Canada Research Chair, Global Control of HPV related cancer*

It is now over a decade since voluntary school-based HPV vaccination commenced in BC in 2008. The HPV vaccination program started with the 4-valent vaccine, protecting against HPV types 6, 11 (responsible for 90% of anogenital warts), and 16, 18 (responsible for 70% of cervical cancers), for girls in grade 6. There was also a 3-year catch-up program for girls in grade 9. In 2014-15, the vaccine schedule changed from a 3-dose to a 2-dose schedule, based on results from a large Canadian trial.[1] In September 2016, the program replaced the 4-valent, with the 9-valent vaccine, which offered protection against 5 additional high-risk HPV types (HPV 31, 33, 45, 52, 58), accounting for about 15% of cervical cancers. These additional 5 HPV types also account for approximately 11% of anal cancers in females and 4% in males. In 2017, the program was expanded to include grade 6 boys.

To date, millions of doses of the HPV vaccine have been administered globally – and it is increasingly evident that HPV vaccination is safe and effective. A 2018 review with over 2.5 million vaccinated individuals showed an acceptable safety profile for HPV vaccines with no consistent evidence of an increased risk of any adverse events of special interest.[2] The most common side-effect is pain or redness at the injection site. The risk-benefit profile for HPV vaccines is highly favourable.

Research has also demonstrated long-term immunogenicity and efficacy of HPV vaccines. A Cochrane systematic review reported that HPV vaccines offered excellent protection against cervical intraepithelial neoplasia grade 2 or 3 and adenocarcinoma in situ associated with HPV16/18 infection.[3] A 2014 study found that girls vaccinated against HPV remained seropositive to HPV-16/18 with antibody titers staying several folds above natural infection levels up to 9.4 years.[4] Here in BC, a data linkage was conducted using records from the Cervix Screening and Immunization registries. Precancerous outcomes were compared between unvaccinated and HPV-vaccinated women. Findings demonstrated that women vaccinated against HPV have a lower incidence of cervical dysplasia compared to unvaccinated women.[5]

Despite this mounting body of evidence demonstrating safety and efficacy, the HPV vaccine's uptake rates have not been as high in BC as for other vaccines offered in grade 6. The uptake rate of the HPV vaccine since 2008 averages 66%, whereas uptake of the Hepatitis B vaccine over the last 10 years is 89%.[6] Improved uptake of the HPV vaccine in the population has the potential to decrease not only cervical dysplasia and cervical cancer rates, but other HPV related diseases such as recurrent respiratory papillomatosis, anogenital warts, oropharyngeal cancers, and other anogenital cancers in both males and females. The reasons for decreased uptake of this vaccine are varied and complex. The hope is that as more of the public becomes aware of the safety and effectiveness of the HPV vaccine against multiple HPV related diseases, and confidence in the vaccine increases, uptake rates across BC will improve. Health practitioners, including primary care, have a critical role in promoting vaccine uptake, and sharing the safety and effectiveness of the HPV vaccine can go a long way to offering increased vaccine confidence to parents.

*Contact Laurie Smith at laurie.smith@bccancer.bc.ca*

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*Hereditary cancer program updates continued from page 8*

## New and Improved Referral Form

After collecting input from a range of referring providers, we expect to launch a new HCP Referral Form very soon. Available at www.bccancer.bc.ca/health-professionals/clinical-resources/hereditary-cancer, the new form will be a fillable PDF that can also be printed and completed by hand. It will include the most common referral indications on the first page, with direction to attach a referral letter/medical records for other indications. The new referral form will also contain a 2-page family history form (to be completed by the patient) to reduce the number of steps in our referral process. Receiving complete information at the time of referral will

*continued on page 10*

# Nasopharyngeal cancer: primary care primer

*By Dr. Eric Tran, Radiation Oncologist, BC Cancer – Vancouver*

Nasopharyngeal carcinoma is the principal tumour type arising in the nasopharynx, the upper part of the throat, which sits behind the nasal cavity (see figure). It is endemic in Southeastern Asia (including Hong Kong and Guangzhou), where the predominant histology is non-keratinizing or undifferentiated carcinoma (WHO type 2 or 3), with age-standardized rates of 25 cases per 100,000 per year. Risk appears to be multifactorial, including Epstein-Barr virus (EBV) infection, environmental/dietary factors (preserved foods, smoking), and genetic predisposition. In North America, nasopharyngeal carcinoma is less common and tends to be WHO type 1 (keratinizing, tobacco-associated). An exception is in areas where there is a large population of Asian ethnicity (Vancouver, San Francisco, Toronto), where the incidence and histology are more similar to that seen in Asia.

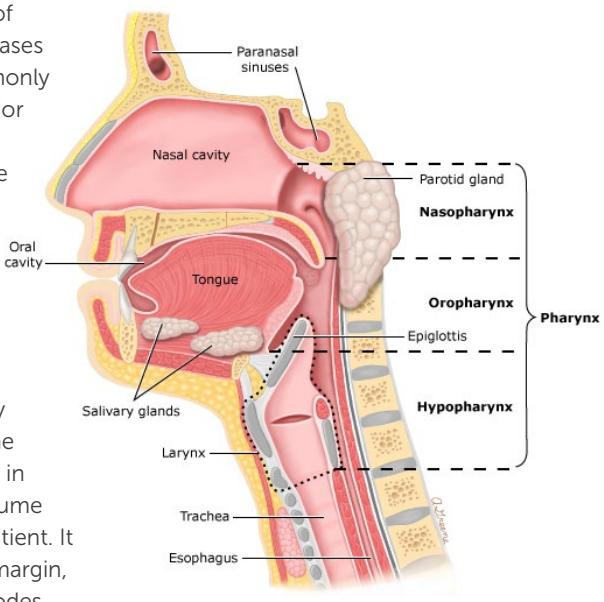
View the full 2019 webcast on this topic at www.fpon.ca – Continuing Medical Education.

Common presenting symptoms include unilateral hearing loss, neck mass, nasal stuffiness/bleeding, headache and cranial nerve palsies. Tumour may spread by direct extension into neighbouring structures. Superior spread into foramen lacerum or ovale often results in damage to cranial nerves VI, V and occasionally III. Postero-lateral spread into the parapharyngeal space is common and may lead to lower cranial nerve palsies. Blindness may be a late presentation if the tumour invades the optic nerve.

The nasopharynx has a rich supply of lymphatics, and lymph node metastases are common at presentation, commonly affecting the jugulodigastric, posterior cervical and retropharyngeal lymph nodes. A definitive diagnosis is made with endoscope-guided biopsy of the nasopharyngeal tumour, with or without biopsy of suspicious nodes. Staging examinations include CT, MRI and PET-CT.

As nasopharyngeal carcinomas are considered radiosensitive (especially WHO type 2 or 3), radiotherapy is the main curative treatment, with doses in the 66-70Gy range. The precise volume to be irradiated is unique to each patient. It typically consists of tumour with a margin, involved lymph nodes and lymph nodes at risk of harbouring disease. Due to the proximity of the tumour to a number of critical structures (optic nerve, chiasm, temporal lobe, brainstem, spinal cord), meticulous treatment planning is essential to avoid exceeding organ tolerance. Toxicity of radiotherapy has improved with modern techniques such as IMRT (intensity modulated radiotherapy). Chemotherapy (cisplatin) is often used concurrently with radiotherapy to enhance local control and cure rates. It can also be used prior to radiotherapy as induction with gemcitabine, particularly if there is significant juxtaposition of the tumour to critical structures. Surgery is not used as first-line treatment due to the deep anatomical location. However, neck dissection may be indicated for residual nodal disease or isolated neck recurrence.

For early and intermediate stage disease, excellent (>90%) locoregional and overall survival rates are achieved. Post-treatment surveillance for 5-7 years is important for early detection of recurrent local or metastatic disease. Follow-up includes periodic nasopharyngolaryngoscopy and neck exam, as well as evaluation of systemic complaints. Patients with local recurrence may be considered for repeat external beam radiotherapy, brachytherapy or surgery, while regional nodal recurrence is usually managed with therapeutic neck dissection. Distant metastatic disease can occur in 15-20% of patients, particularly with extensive nodal disease.

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*Contact Dr. Eric Tran at etran2@bccancer.bc.ca*

*Hereditary cancer program updates continued from page 9*

support more efficient assessment and follow-up for those with hereditary cancer concerns.

## Virtual Appointments

As a provincial program, the Hereditary Cancer Program staff have provided service via video-conference and telephone for many years. That meant we were well-prepared for changes required with COVID-19. All genetic counselling appointments were held by phone in the initial phases of our pandemic response, and mostly by staff working from home. We also began to offer individual and family group appointments using Zoom for Healthcare with very positive feedback from both patients and clinicians. We hope that experience will support our future use of Zoom to provide group sessions for unrelated patients.

## Hereditary Cancer Follow-up Initiative

A current Hereditary Cancer Program priority is to reconnect with everyone in BC/Yukon identified to carry a hereditary cancer gene mutation. Our initial survey aims to obtain health updates, and learn about challenges with access to recommended cancer screening and unmet information or support needs. The information will help identify priorities for ongoing follow-up and support of families living with hereditary cancer risk in BC/Yukon.

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# Corridor Consult – prostate cancer screening

*By Drs. Raziya Mia and Sian Shuel, former and present Medical Lead, Education, Family Practice Oncology Network, with Dr. Michael Peacock, Radiation Oncologist, BC Cancer – Vancouver*

**Multiple questions arose following BC Cancer's Family Practice Oncology Network spring webcast on Prostate Cancer. A summary follows below:**

## Q1 What is the current BC recommendation on PSA testing for prostate cancer (PCa) screening in average risk men?

**Prostate Specific Antigen (PSA) testing may be considered in asymptomatic men aged 55-69 with a greater than 10-year life expectancy. Informed choice discussion is essential, and detailed guidance can be found in the Primary Care Prostate Cancer Guideline newly published by BC Cancer's Family Practice Oncology Network and the BC Guidelines and Protocols Committee: www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines**

Accredited, case-based learning:
BC Cancer Primary Care Learning Session – Prostate Cancer
ubccpd.ca/oncology/primary-care

*Note: If PSA level is within the appropriate age-based reference range, further testing in less than two years is not indicated.*

**Age-based Reference Range for PSA Test Results***

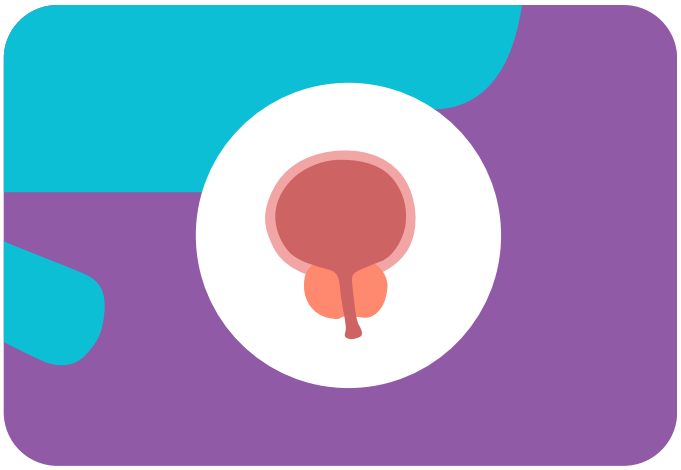
| Age | PSA Reference Ranges |
|---|---|
| 0 - 49 | 0 - 2.5 ng/ml |
| 50 - 59 | 0 - 3.5 ng/ml |
| 60 - 69 | 0 - 4.5 ng/ml |
| ≥70 | 0 - 6.5 ng/ml |

**There may be individual laboratory variation.*

## Q2 What is the role of digital rectal exam (DRE) in asymptomatic men?

The use of DRE for prostate cancer screening in asymptomatic men is controversial. There are recommendations both for and against. Like with PSA testing, offering an informed discussion of the harms and benefits is essential. Benefits of DRE include the potential identification of significant PCa in asymptomatic men independent of PSA level. However, the accuracy of DRE as a diagnostic tool for PCa has limited application, with a low predictive value when evaluated against biopsy. DRE has a poor sensitivity and specificity, high inter-observer variability, and may contribute to unnecessary biopsies.

*Note: Any abnormal finding on DRE warrants urgent referral to a urologist regardless of PSA level.*



## Q3 How does a positive family history of PCa influence the decision to screen?

Factors associated with an increased risk of PCa include:

- Family history of a first-degree relative with PCa;
- Family history of high-risk germline mutations, in particular BRCA2 in a first degree relative;
- Men of African descent.

*Note: Men at higher risk of developing PCa may consider PSA testing as early as 40-45 years of age and re-testing every 2 years.*

## Q4 What are the benefits and risks associated with prostate cancer screening?

Studies are ongoing and have shown a risk reduction in PCa mortality with screening. A decrease in morbidity has also been found, with less pain and suffering related to metastatic disease. Modeling studies suggest the benefits may be greater when extrapolated over a patient's lifetime. Risks of screening asymptomatic men include potentially harmful investigations and treatment, particularly in those who may not benefit. Needle biopsy complications can include pain, bleeding, and infection. Treatment-related morbidities, such as erectile dysfunction and urinary incontinence, can have a major impact on quality of life.

*Note: In appropriate patients diagnosed with prostate cancer through screening, active surveillance can mitigate the harms associated with treatment.*

## Q5 What symptoms should prompt investigation for prostate cancer?

While there is an absence of highly predictive signs and symptoms of prostate cancer, new onset lower urinary tract symptoms warrant investigation. Additional symptoms may include hematospermia, erectile/ejaculatory dysfunction, pelvic pain, pedal edema, change in bowel habit, bone/back pain, unexplained weight loss, and fatigue.

*Note: Most patients with early stage prostate cancer do not experience clinical symptoms.*

## Q6 Does 5-alpha reductase inhibitor use affect PSA level?

PSA will drop by approximately 50% in men taking 5-alpha reductase inhibitors (finasteride and dutasteride).

*Note: In patients on 5-alpha reductase inhibitors, adjust lab reported age-based ranges by a factor of two.*

## Q7 What other conditions can increase PSA?

Additional causes of elevated PSA include urinary retention, prostatitis, benign prostatic hyperplasia (BPH), and bladder catheterization/instrumentation.

*Note: PSA levels are not significantly altered after cycling, intercourse, or DRE.*

*Contact Dr. Michael Peacock at michael.peacock@bccancer.bc.ca*

# Bladder cancer for family physicians

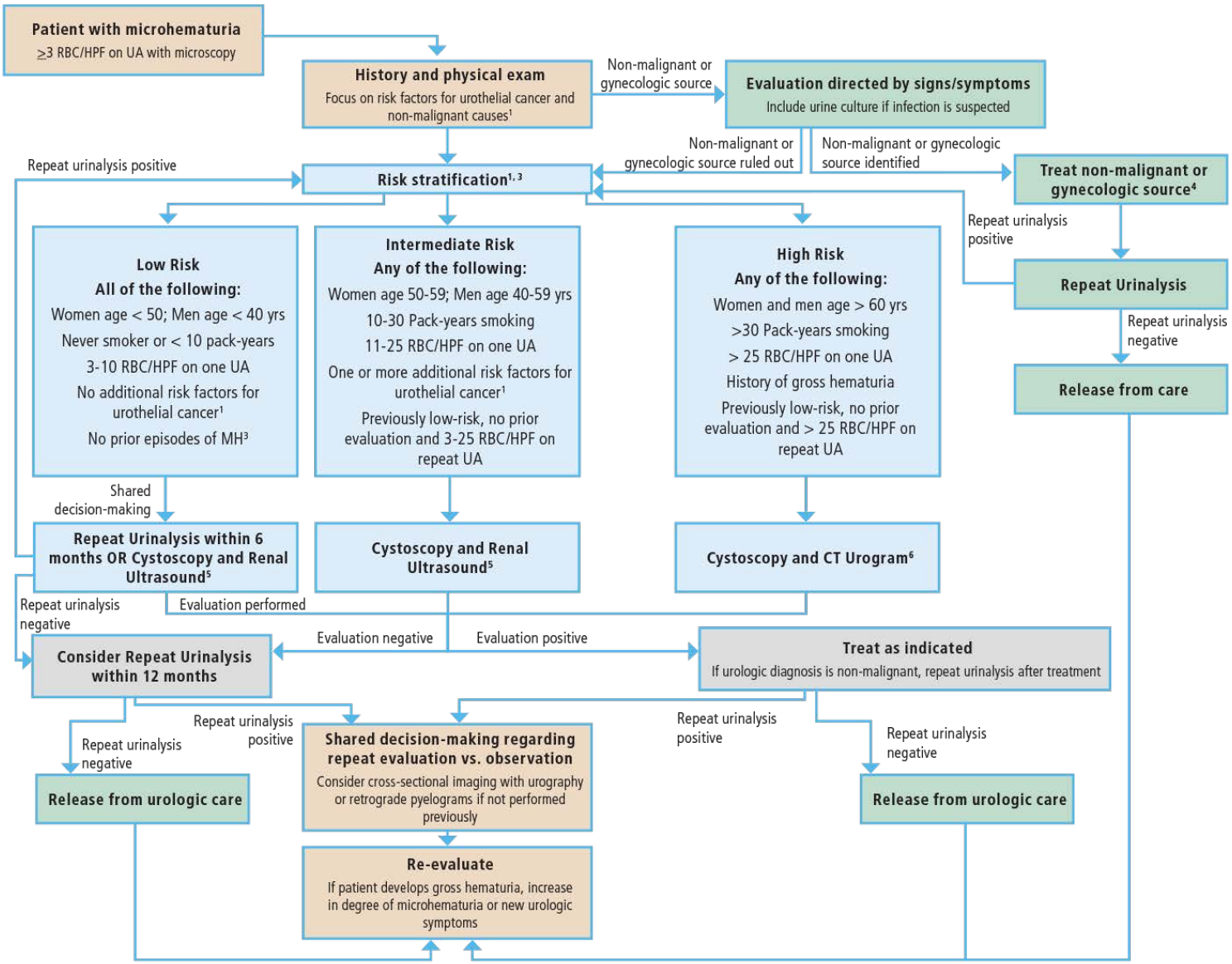
*By Dr. Michael J. Metcalfe, Victoria Urologist, Member, Society of Urologic Oncology*

Bladder Cancer is the 5th most common malignancy and accounted for 11,800 new cases in Canada in 2019.[1] Due to its nature, with 70% presenting as non-muscle invasive bladder cancer (NMIBC), it is associated with a long disease course and multiple procedures, making it the most costly cancer to care for per patient.[2] From first diagnosis, to end of life, and involvement of every step in between, the family physician's role is critical to help guide their patients through their journey with bladder cancer.

The most common presenting symptom for bladder cancer is hematuria. However, currently, there are no accepted screening tests for hematuria and urine microscopy is not routinely recommended for asymptomatic patients, despite the presence of risk factors. Microhematuria, defined as >2 RBC/HPF on microscopy, can be found in 6.5% (2.4-31.1%) of healthy individuals. It is associated with cancer 3.1% of the time.[3]

The American Urological Association guidelines for **microhematuria** were recently updated by a multidisciplinary panel.[4] The guidelines are outlined in **figure 1** and are summarized below:

*continued on page 13*




1. Main risk factors for urothelial cancer are those in the AUA risk stratification system (age, male sex, smoking, degree of microhematuria and history of gross hematuria). Additional risk factors for urothelial carcinoma include but are not limited to irritative lower urinary tract voiding symptoms, history of cyclophosphamide or ifosfamide chemotherapy, family history of urothelial carcinoma or Lynch Syndrome, occupational exposures to benzene chemicals or aromatic amines, history of chronic indwelling foreign body in the urinary tract
2. If medical renal disease is suspected, consider nephrologic evaluation, but pursue concurrent risk-based urological evaluation
3. Patients may be low-risk at first presentation with microhematuria, but may only be considered intermediate- or high-risk if found to have persistent microhematuria
4. There are non-malignant and gynecologic sources of hematuria that do not require treatment and/or may confound the diagnosis of MH. Clinicians can consider catheterized urine specimen in women with vaginal atrophy or pelvic organ prolapse. Clinicians must use careful judgment and patient engagement to decide whether to pursue MH evaluation in the setting of chronic conditions that do not require treatment, such as the aforementioned gynecologic conditions, non-obstructing stones or BPH.
5. Clinician may perform cross-sectional imaging with urography or retrograde pyelograms if hematuria persists after negative renal ultrasound
6. MR Urogram or Non-contrast imaging plus retrograde pyelograms if contraindications to CT Urogram

Figure 1 – Algorithm associated with Microhematuria: AUA/SUFU Guideline[4]

*Bladder cancer for family physicians continued from page 12*

- If microhematuria could be attributed to a known cause other than a malignancy, clinicians should repeat urinalysis following the resolution of the known cause.
- If microhematuria persists or the etiology cannot be identified, clinicians should categorize risk as either low, intermediate or high.
- Risk factors for malignancy include: age, male sex, smoking, degree of microhematuria, persistence of microhematuria and history of gross hematuria as well as irritative urinary symptoms, prior pelvic radiation, prior cyclophosphamide chemotherapy, history of urothelial cancers, Lynch syndrome, chronic indwelling foley catheters, exposure to benzenes, or aromatic amines.
- **If deemed low risk**, perform either cystoscopy and renal ultrasound, OR repeat urinalysis in 6 months.
- **If deemed intermediate risk**, perform cystoscopy AND renal ultrasound
- **If deemed high risk**, perform cystoscopy and CT-Urogram.

**Gross hematuria** is associated with bladder cancer 13% of the time, and its workup is more defined . The presence of other potentially causative factors such as UTI, anti-coagulation or kidney stones does not mitigate the need for a complete evaluation. A complete gross hematuria evaluation consists of upper tract imaging with CT or ultrasound, urine cytology and urgent referral to Urology for cystoscopy.

If a bladder cancer diagnosis is made by imaging or cystoscopy, an expedient transurethral resection of bladder tumour (TURBT) is recommended to stage and diagnose bladder cancer. For NMIBC, which is the case 70% of the time, the TURBT is followed by surveillance and use of intravesical agents such as BCG to prevent disease recurrence. NMIBC, in its lowest risk setting, has a 40% recurrence rate and warrants regular cystoscopy with urine cytology with prolonged follow up, up to 10 years.[6] The other 30% of bladder cancer is muscle invasive (MIBC), and treatment consists of chemotherapy, radical cystectomy and/or radiation therapy. Despite aggressive management, MIBC carries a 50% 5-year survival rate. It is recommended that patients get an assessment at a higher volume centre from both a urologist with high volume bladder cancer care, and at least one medical oncology or radiation oncology consultation.

*Contact Dr. Michael Metcalfe at michaelmetcalfe5@gmail.com*

## Key points

Screening Recommendations:

- There is no role for routine screening for bladder cancer with imaging or urinalysis/microscopy in asymptomatic individuals.

Microscopic Hematuria: Should be classified into risk groups.

- Low Risk: repeat urinalysis in 6 months OR cystoscopy and ultrasound
- Intermediate Risk: cystoscopy and renal ultrasound
- High Risk: cystoscopy and CT urogram

Gross Hematuria: Workup is uniform despite other potential causes.

- Cystoscopy, urine cytology and CT urogram or ultrasound

Surveillance recommendations for treatment of non-muscle invasive bladder cancer.

- Cystoscopy at three months following a TURBT where a diagnosis of non-muscle invasive bladder cancer is made.
- Generally, cystoscopy with cytology is recommended every three months for 2 years, then every six months for 2 years then annually for 5 years. Patients with low risk tumours may have one cystoscopy at 3 months and then annually.
- Upper tract imaging through CT or ultrasound is recommended for all patients with high risk non-muscle invasive bladder on an annual basis.

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*Hereditary cancer program updates continued from page 10*

## Current Options for Private Pay Genetic Testing

The Screen Project is a Canadian initiative, based at Women's College Hospital in Toronto to evaluate the benefits of a population-based approach to genetic testing. This research study offers BRCA1 & BRCA2 testing to Canadian adults at an accessible price ($250 US) and may be an option for people who do not meet current provincial criteria for funded genetic testing, or who seek more timely access to BRCA1/BRCA2 test results. Any BC/Yukon resident who receives a positive result will be referred by the study team to the Hereditary Cancer Program for local follow-up. Visit www.thescreenproject.ca/ for more information and study registration.

Alternately, Color Genomics (www.color.com/t/welcome) and Invitae (www.invitae.com/en/) offer broader panels of hereditary cancer genes at similar cost for those who may be interested.

*Contact Mary McCullum at mmccullum@bccancer.bc.ca or Jennifer Nuk at jnuk@bccancer.bc.ca.*

# Immune checkpoint inhibitors: a team approach to care

*By Dr. Sian Shuel, Medical Lead, Education, Family Practice Oncology Network, and Dr. Muhammad Zulfiqar, Medical Oncologist, BC Cancer – Abbotsford*

*Mr. C is a 59-year old male with a history of renal cell carcinoma. He presents to his family physician, Dr. F, with a 5-day history of grade 2 diarrhea, despite taking loperamide regularly for three days. He reports he started 'chemo' 6 weeks ago. Dr. F reviews Mr. C's chart and clarifies that Mr. C is receiving nivolumab. Dr. F recalls nivolumab is not cytotoxic chemotherapy, but rather a type of immunotherapy, specifically an immune checkpoint inhibitor (CPI). Dr. F knows this treatment distinction has important implications for management and patient outcome.*

## Background

Immunotherapy, such as CPIs, has significantly improved prognosis for patients with many advanced cancers[1]. It is used with increasing frequency, in the management of various tumour types including renal cell carcinoma, melanoma, non-small cell lung cancer, urothelial carcinoma, squamous cell carcinoma of head and neck, Hodgkin lymphoma, and Merkel cell carcinoma. As front-line healthcare providers, family physicians play an integral role in recognizing and managing immune-related adverse events (irAEs).

## Mechanism of Action

Immune checkpoint proteins help regulate the immune response. The immune checkpoint proteins PD-1 and CTLA-4 are found on T cells. When bound, they transmit suppressive signals to T cells. More specifically, healthy cells have proteins called PD-L1 that bind with PD-1 on the T cell. The binding of PD-L1 to PD-1 sends an inhibitory message to the immune system preventing the immune system from attacking healthy cells. However, some cancer cells can also express PD-L1, which binds to PD-1 on T cells, preventing the T cell from attacking the cancer cell (figure 1a)[2].

The binding of the ligand B7, produced by normal cells and by some tumour cells, to the checkpoint protein CTLA-4 sends inhibitory signals to the T cell (figure 1b)[2].

CPIs (such as PD-1 inhibitors, PD-L1

*continued on page 15*

# Lidocaine infusions and severe cancer pain

*By Dr. Pippa Hawley, Medical Lead, BC Cancer Pain and Symptom Management/ Palliative Care Program*

Dr. Pippa Hawley

The vast majority of cancer pain can be relieved with regular opioids and orally administered adjuvant analgesics. Interventions such as radiotherapy and palliative procedures are also sometimes possible and highly effective. There remains, however, a small group of cancer patients for whom none of these interventions provide adequate pain control. Approximately half of these patients may benefit from lidocaine infusion.

Lidocaine can be administered intravenously or subcutaneously, on an intermittent or continuous basis. For those living at home, an intermittent intravenous bolus can provide surprisingly durable pain relief. Once the blood level of lidocaine reaches a threshold blood level, it reduces firing of damaged nerves providing pain relief. In those with severe chronic pain and secondary sensitization, ("wind-up") lidocaine "resets" the nervous system via mechanisms that are complex and not yet fully understood.

Lidocaine causes blood-level-dependent side-effects, specifically tingling and numbness around the mouth occurring at lower levels than serious side-effects. As long as a patient is awake, and able to report these effects, and observed closely throughout the infusion by someone who knows what to look for, any potentially toxic rise in blood level can be identified, and the infusion stopped or slowed, ensuring safe completion.

Despite lidocaine infusions having been shown to be safe, and not require electrocardiographic monitoring, they are unavailable in most care settings. Lidocaine is associated in people's minds with a need for monitoring because of its historical use in suppressing cardiac arrhythmias during/ after heart attacks. This is a challenging perspective to overcome.

With support from the BC Cancer Foundation, Dr. Pippa Hawley and BC Cancer – Kelowna colleagues, Gillian Fyles and Steve Jefferys, recently published the results of a clinical trial on lidocaine administered subcutaneously through a "butterfly" plastic cannula under the skin. The idea was that if this was successful, then patients might be able to access lidocaine infusions at home, in hospice, on general medical wards, or anywhere that did not provide access to intravenous infusions in general or to lidocaine in particular.

The results of the study were interesting, and despite not showing an overall benefit to participating patients, the effort proved useful. We found that the predictability of blood level with a standard weigh-based calculation (10 mg/kg administered over 5 and a ½ hours) produced a wide range of blood lidocaine levels, mostly sub-therapeutic. In a couple of patients, however, the level did reach a clinically relevant, but not toxic level. The study therefore demonstrated that 10mg/kg over 5 and a ½ hours is a safe starting dose, but one that would most likely be ineffective in the majority of patients. As a potential solution, infusions could be repeated at intervals with an increasing dose until an individual either benefited, or experienced lidocaine-specific side-effects indicating that a potentially therapeutic dose had been reached. We hope that this information facilitates access to good pain relief for the most complex cancer pain syndromes.

*Contact Dr. Pippa Hawley at phawley@bccancer.bc.ca*

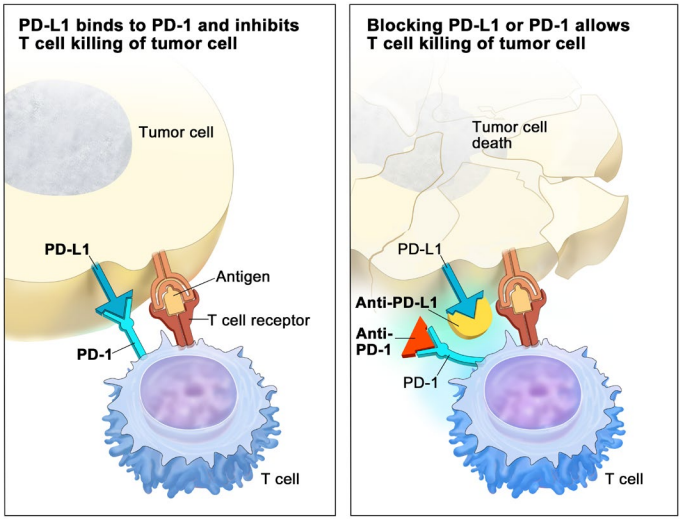




Figure 1a Immune Checkpoint Inhibitor (PD-1)

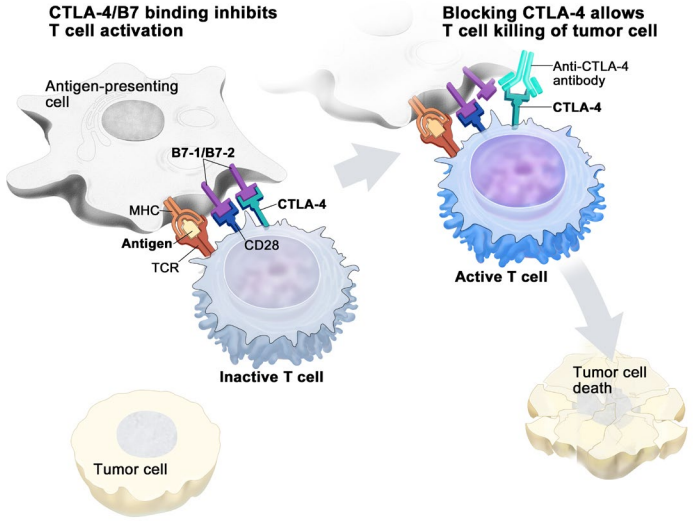




Figure 1b Immune Checkpoint Inhibitor (CTLA-4)

*Immune checkpoint inhibitors continued from page 14*

inhibitors and CTLA-4 inhibitors) block this binding, allowing the T cell to recognize and attack the cancer cell. Examples of PD-1 inhibitors include nivolumab and pembrolizumab. Durvalumab and avelumab are PD-L1 inhibitors, while ipilimumab is a CTLA-4 inhibitor.

## Adverse Events

As previously noted, immune checkpoint proteins are present not only on cancer cells but also on healthy ones. Inhibiting the suppressive signal between T cells and other healthy cells can lead to irAEs[3]. This inflammatory process (often referred to the '-itises') occurs most frequently in the colon (colitis), skin (dermatitis), liver (hepatitis), lungs (pneumonitis) and endocrine systems (thyroiditis, hypophysitis, etc.)[4]. However, irAEs can affect any body system (figure 2) and can have life-threatening consequences.

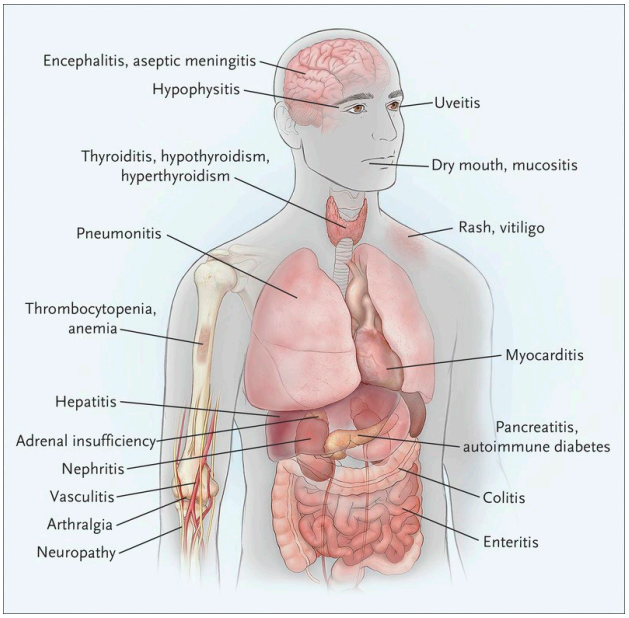


Figure 2: Organs Most Commonly Affected by Immune-Related Adverse Events.

Postow M, Sidlow R, Hellmann M. Immune-related adverse events associated with immune checkpoint blockage. N Engl J Med 2018; 378:158-168.

## Timing

IrAEs often start within the first few weeks of treatment initiation. However, they can occur at any time, including after discontinuation of treatment. IrAEs have been documented as late as 1-year post discontinuation of the CPI[5].

## Management and Case Outcome

Management of irAEs often requires high-dose steroids to counteract inflammation and slow down the autoimmune insult on organs.

*Dr. F recalls a useful protocol (SCIMMUNE protocol) on BC Cancer's website at bccancer.bc.ca[6] for an approach to managing irAEs. She plans to rule out infectious causes of diarrhea and, after reviewing the potential risks and benefits, prescribe prednisone 0.5 – 1mg/kg/day PO (if grade 3+ diarrhea develops give prednisone 1-2mg/kg/day PO). Dr. F speaks to the patient's medical oncologist, Dr. M, relaying the history and plan. Dr. M appreciates the phone call, and as a result, he will withhold the CPI and follow up with Mr. C. The plan is to taper the prednisone over one month before resuming the CPI.*

*Contact Dr. Sian Shuel at sian.shuel@bccancer.bc.ca*

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# Immune checkpoint inhibition in renal transplant recipients: a precision-medicine guided approach to multidisciplinary care

*Dr. Sanjay Rao, Medical Oncologist, BC Cancer – Kelowna, Dr. Christopher Blosser, Clinical Associate Professor, Division of Nephrology, University of Washington, and Dr. James Lan, Transplant Nephrologist, Vancouver General Hospital*

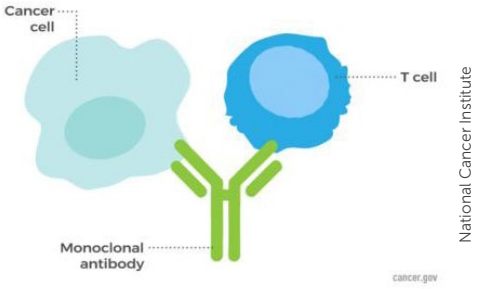
Researchers from the University of Washington, the renal transplant group in Vancouver, and BC Cancer are collaborating on an upcoming study to optimize the care of kidney transplant recipients (KTRs) who may be eligible for immune checkpoint inhibitor (CPI) therapy, a type of immunotherapy for the management of malignancy. The precision-medicine component of the study, guided by nephrologist and principal investigator, Dr. Chris Blosser of the University of Washington, and Dr. James Lan of Vancouver General Hospital, will employ cell-free DNA (cfDNA) assays to assist in the earlier identification of signs of rejection and malignancy recurrence, with the goal of improving graft- and malignancy-related outcomes.

KTRs, like patients with end-stage renal failure, are at elevated risk of cancer compared with the general population.[1] The increased risk is largely due to the immunosuppressive effects of dialysis and immunosuppressive medications, the latter of which are required to prevent transplant graft rejection. The risk of certain cancers, including cutaneous squamous, lung, and kidney, may be notably increased among KTRs.[2]

Further, patient survival on the kidney transplant waitlist has improved over time, most notably for individuals over 55 years of age.[3] Hence older patients comprise an increasing proportion of KTRs, and they are living longer after transplantation.[3]

Contemporary health care has improved post-transplant disease management, resulting in longer graft survival as well as a decrease in overall mortality and mortality related to two of the leading causes of death — cardiovascular disease and infection.[3] Cancer is the second or third leading cause of death in KTRs.[4, 5]

The last decade has led to the promising application of immunotherapies in the management of malignancy.[6] CPIs, which function by activating or reactivating immune system T cells, are a group of highly effective immunotherapies for treatment of many solid tumors.[7] Unfortunately, this T cell activation or reactivation can cause graft rejection, and CPI use in organ transplant recipients has resulted in rejection in 37-50% of cases.[7,8]



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Most family physicians are aware of the special considerations, such as the increased risk of infection due to immunosuppression, involved in the care of KTRs diagnosed with malignancy and treated with conventional chemotherapy. Immunotherapy, such as CPIs are not generally associated with immunosuppression. However, given the immune system activation associated with CPIs, there is still a need for close collaboration with a transplant nephrologist to evaluate the risk of injury to the graft, and monitor for rejection when CPI therapy is initiated.

Therefore, in addition to improving graft- and malignancy-related outcomes, another goal of this study is to create a true multidisciplinary collaboration to streamline engagement with the renal transplant group (represented by Dr. James Lan at Vancouver General Hospital and Dr. John Gill at St. Paul's Hospital) for KTRs who are eligible for CPI therapy.

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ISSN 2369-4165 (Print)
ISSN 2369-4173 (Online)
Key title:
Journal of family practice oncology

Publications Mail Agreement Number 41172510

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