Cancer diagnosis in primary care

Six steps to reducing the diagnostic interval

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Primary care providers (PCPs) diagnose approximately 1 cancer per month. However, for each malignancy identified, PCPs evaluate many other patients presenting with potential symptoms of cancer.[1] Thresholds for investigation must balance resource use and adverse effects from diagnostic and incidental findings with the risk of missing or delaying a diagnosis of malignancy. A lengthening of the diagnostic interval (**Figure 1**)[2] can occur because of cognitive errors on the part of the physician, lack of timely access to tests, and lags in patient presentation influenced by knowledge, social context, and beliefs.[3] Such delays can irreparably fracture the patient-physician relationship at a time when medical support is most required. This article provides a 6-step guide (**Figure 2**) to help PCPs decrease the diagnostic interval and enable a more positive patient outcome.

Step 1: history

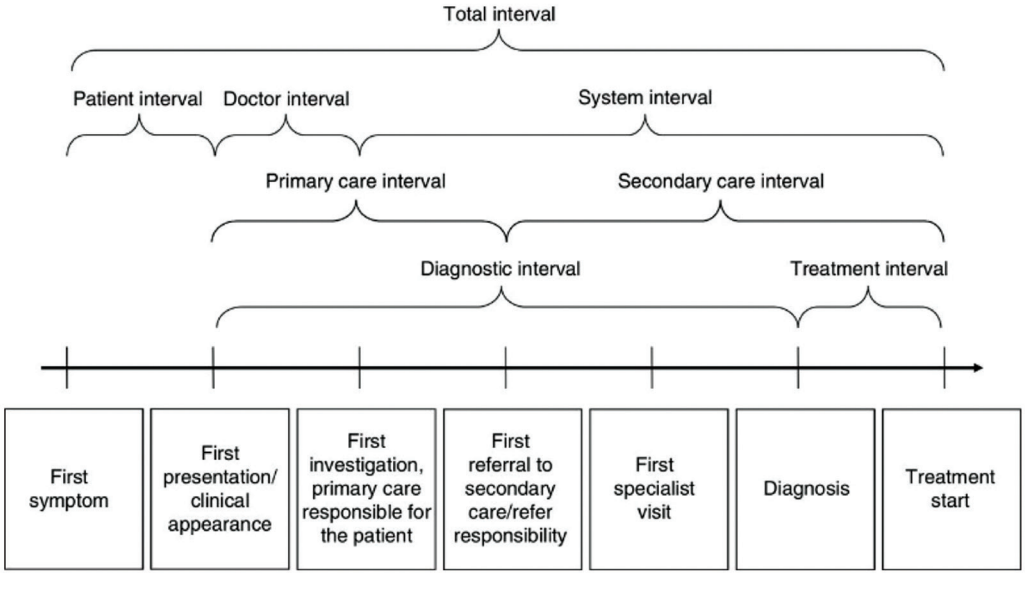
Diagnostic workups for cancers are commonly initiated when patients present with local or systemic symptoms. Many of these concerns, such as hemoptysis, dysphagia, breast lumps, and postmenopausal or rectal bleeding, obviously require workup; however, others like fatigue, headache, change in bowel habits, and abdominal pain or distension, are subtle "low risk, but not no risk" symptoms also present in benign conditions.[1] A physician's clinical acumen and knowledge of the patient's medical history and risk factors (such as smoking, family history, and obesity) are critical in determining the threshold for further investigation.

The risk of a patient having a cancer when presenting with symptoms to their family physician has been determined retrospectively and can help inform management (**Table 1**).[4,5] Certain symptoms have a greater association with the diagnosis of malignancy, triggering a more in-depth examination. Patients who present with the same symptoms on numerous occasions and those who present with multiple symptoms concurrently are at greater risk of malignancy (**Table 2**).

Step 2: physical examination

With any suspicion of malignancy, a methodical, head-to-toe physical examination is required to determine a possible primary site and delineate the extent of disease. Clinical history should direct examination, with a specific focus on identifying the likely area of the primary malignancy. Performing lymph node examination is useful, as the presence of nodal disease can help to clinically determine the disease stage or lead to the location of an unknown primary cancer. Characteristics of lymph nodes can help to differentiate benign from malignant nodes, as

Figure 1. Diagnostic interval



Adapted from Kanguru et al.[2]

Figure 2. Six steps to reduce cancer diagnostic interval

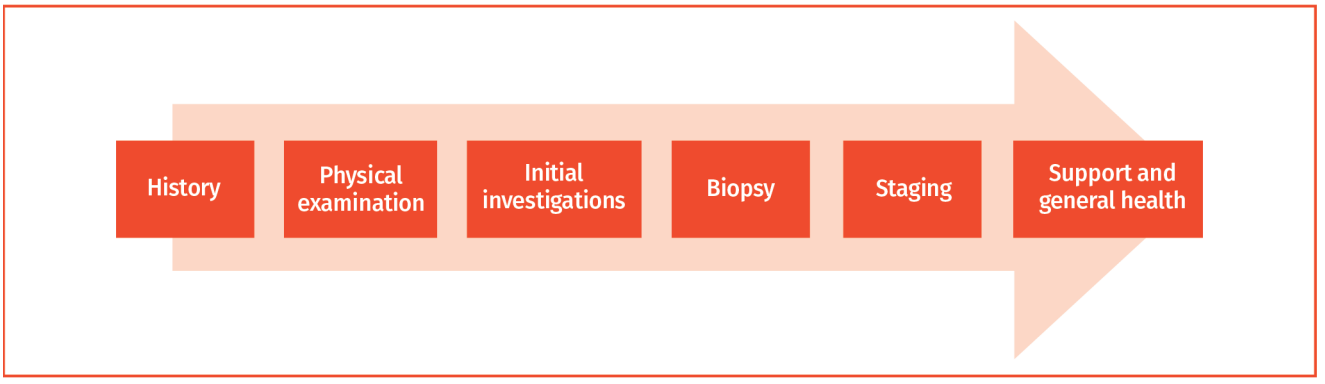


Table 1. Cancer symptom PPV

TYPE OF CANCER	SYMPTOM	PPV
Colon cancer	Constipation	0.42
	Diarrhea	0.94
	Abdominal pain	1.1
	Abdominal tenderness	1.1
	Weight loss	1.2
	Rectal bleeding	2.4
Lung cancer	Cough	0.40
	Fatigue	0.43
	Dyspnea	0.66
	Chest pain	0.82
	Loss of appetite	0.87
	Weight loss	1.1
	Hemoptysis	2.4
Prostate cancer	Weight loss	0.75
	Hematuria	1.0
	Nocturia	2.2
	Frequency	2.2
	Urgency	3.0

PPV—positive predictive value.
Data from Hamilton[4] and Del Giudice et al.[5]

Table 2. Recurrent or multiple symptoms of cancer PPV

SYMPTOM	PPV
Abdominal pain with 1 presentation	1.1
Abdominal pain with repeat presentation	3.0
Abdominal pain and loss of weight	3.4

PPV—positive predictive value.
Data from Hamilton.[4]

those indicative of malignancy tend to be painless, hard, and greater than 2 cm. A broader physical examination can also identify features suggestive of metastatic disease such as masses, jaundice, pleural effusions, hepatomegaly, ascites, and raised intracranial pressure.

Step 3: initial investigations

Abnormalities in laboratory findings can indicate the presence of a cancer, metastasis, or paraneoplastic syndrome (**Box 1**). To anticipate a possible biopsy, order an international normalized ratio test and a complete blood count to document platelet count. It is important to know the baseline creatinine level for patients who will be undergoing imaging requiring contrast.[6]

Tumour markers are substances produced by either cancer cells or the host in response to the presence of cancer. These markers are a heterogeneous group of molecules, including hormones (β-human chorionic gonadotropin), enzymes (prostate-specific antigen), proteins and glycoproteins (cancer antigen 125), and oncofetal antigens (carcinoembryonic antigen and α-fetoprotein). Tumour markers range widely in sensitivity and specificity for different cancers and can be elevated in benign conditions. They can facilitate diagnosis when ordered to investigate a specific malignancy or unknown primary tumour, but should not be ordered indiscriminately (**Table 3**).[7] Tumour markers can be useful to follow a known cancer to assess treatment response or during survivorship care for disease recurrence.[6]

Imaging results will confirm the presence of malignancy and determine the best site for a biopsy. Unless there is a very high clinical suspicion of cancer, the least invasive test with the lowest radiation exposure should be ordered. A diagnostic mammogram and breast ultrasound are indicated if breast cancer is suspected. A chest x-ray scan is appropriate for initial investigation of suspected thoracic cancers, and an ultrasound is appropriate for abdominal symptoms and isolated adenopathy. Additional imaging is dictated by radiologic findings.[8] In cases where there is a very high clinical suspicion of malignancy, a computed tomography (CT) scan as initial imaging might be reasonable.[9] Any highly suspicious findings reported on an x-ray scan or ultrasound will require a CT scan before a biopsy.

Step 4: biopsy

Cancer therapy is predicated on accurate knowledge of tumour pathology, and cancer centres require

pathology results to accept referrals. Therefore, it is essential that a biopsy be performed if there is high suspicion of malignancy. Biopsies are ideally performed on the most accessible suspected tumour in order to minimize complications. Alternate means for obtaining pathology results can include excision of involved lymph nodes, cytology from effusions or ascites, or procedures such as endoscopy, bronchoscopy, mediastinoscopy, pleuroscopy, or colonoscopy.[10] Any biopsies that are high risk for bleeding, like solid-organ biopsies, require anticoagulation be managed appropriately (**Box 2**).[11] The Thrombosis Canada perioperative anticoagulation management algorithm is an excellent tool in this regard and can be found at **www.thrombosiscanada.ca**.

Tumour samples must be adequate for histologic examination, immunohistochemical classification (eg, thyroid transcription factor 1), and molecular profiling (eg, epidermal growth factor). Thus, core or excisional biopsies are preferred, as fine needle aspirates might not have enough tissue for complete analysis.

Step 5: staging

Once pathology results are obtained, patients should be referred to the appropriate oncologist. To avoid further delays for patients, appropriate staging investigations should be ordered immediately upon diagnosis. This way, staging is completed or pending by the time the patient sees the oncologist, and treatment can be initiated sooner. Staging investigations must reflect the typical patterns of metastases for the cancer in question, as well as any symptoms that the patient is reporting (**Box 3**).[12] Asymptomatic early-stage breast cancer and prostate cancer do not require staging investigations.[13,14]

Computed tomography scans with contrast are generally used to assess the thorax, abdomen, and pelvis,[15] while bone scans help detect bone metastases. Magnetic resonance imaging (MRI) can have a role in staging rectal and prostate cancers. Brain imaging uses

Box 1. Recommended laboratory workup for diagnosis of malignancy

- Complete blood count
- Creatinine level
- Electrolyte level
- Calcium, magnesium, and phosphate levels
- Liver function test, including albumin level test
- International normalized ratio test
- Lactate dehydrogenase level
- Serum protein electrophoresis, if clinically indicated
- Tumour markers as appropriate

Table 3. Tumour markers

TUMOUR MARKER	CANCER TYPE
CEA	Colon, hepatocellular
Carbohydrate antigen 19-9	Pancreatic, bile duct
Urinary 5-HIAA	Neuroendocrine
Cancer antigen 15-3	Breast
Cancer antigen 125	Ovarian
PSA	Prostate
αFP	Hepatocellular, germ cell
βHCG	Germ cell, gestational trophoblastic
Thyroglobulin	Thyroid

αFP—α-fetoprotein, CEA—carcinoembryonic antigen, βHCG—β-human chorionic gonadotropin, HIAA—hydroxyindoleacetic acid, PSA—prostate-specific antigen.
Data from Bigbee and Herberman.[7]

Box 2. Anticoagulation management before biopsy

- Antiplatelet agents (eg, acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, clopidogrel, ticagrelor)—hold 5 days before
- Warfarin—hold 5 days before until international normalized ratio test results < 1.8; consider bridging with low-molecular-weight heparin
- Direct oral anticoagulants (eg, edoxaban, apixaban)—hold 2 to 3 days before
- Low-molecular-weight heparin—hold 1 dose before procedure if prophylactic, and 2 doses if therapeutic dosing

Data from Patel et al.[11]

Box 3. Recommended staging investigations for common cancers: *All imaging should be done with contrast when possible.*

- Breast
  - -Clinical stage 1 and 2, and asymptomatic (tumour < 5 cm and < 3 nodes involved, or > 5 cm and no nodes)
    - —No staging required
  - -Clinical stage 3 (tumour < 5 cm and > 3 nodes involved, or > 5 cm and nodal involvement)
    - —CT scan of chest, abdomen, and pelvis
    - —Bone scan
- Lung
  - -CT scan of chest, abdomen, and pelvis
  - -Bone scan
  - -CT scan or MRI of brain
- Colon
  - -CT scan of chest, abdomen, and pelvis
- Prostate
  - -Clinically low risk and asymptomatic (tumour nonpalpable, or contained within half of 1 lobe; PSA level < 10; Gleason score ≤ 6)
    - —No staging required
  - -Intermediate or high risk (tumour confined to prostate; PSA level between 10 and 20; Gleason score ≥ 7)
    - —Bone scan
    - —CT scan or MRI of abdomen or pelvis

CT—computed tomography, MRI—magnetic resonance imaging, PSA—prostate-specific antigen.
Data from the National Comprehensive Cancer Network.[12]

either CT scan, which might be easier to obtain, or MRI, which can detect 2 to 3 times more lesions than CT scan, especially those less than 5 mm. Brain MRI is superior for identifying leptomeningeal disease and cranial nerve involvement.[16] Oncologists might further stage malignancies with functional imaging (eg, positron emission tomography scan), which is indicated in select malignancies to determine resectability.[17]

Step 6: support and general health

Initial discussions about diagnosis focus on information sharing, supporting the patient, and expediting time to therapy. Primary care physicians should ensure regular follow-up appointments are scheduled to share results, answer questions, provide ongoing emotional support, address symptoms, and ensure an appropriate management plan. They should also broach other key topics with patients during this process, listed below.

Smoking cessation. A cancer diagnosis can be a substantial impetus to enact change. Patients who smoke during treatment will increase the toxicity of therapy and will decrease the efficacy of treatment. Smoking is associated with an increased risk of recurrence, cancer-specific and overall mortality, and development of a second primary cancer.[18] Family physicians are ideally positioned to be a helpful resource in smoking cessation for these patients at a time when they might be receptive to making lifestyle changes.

Vaccinations. Live vaccinations are contraindicated during chemotherapy, and the efficacy of inactivated vaccines might be compromised. Primary care physicians should work to ensure that all vaccinations are current before cancer therapy is initiated.

Fertility. Cancer therapies, primarily radiation and chemotherapy, can cause premature ovarian failure in 15% to 40% of women younger than 30 years old, and in 49% to 100% of women older than 40.[19] Men can develop impaired spermatogenesis after chemotherapy exposure at rates of up to 90%, depending on the chemotherapy drugs used.[20] In the rush to start cancer therapy, fertility preservation is often compromised. It is incumbent upon PCPs to address fertility preservation with newly diagnosed cancer patients in their reproductive years. By referring expeditiously to fertility centres, patients can have more time for counseling, decision making, and any necessary procedures.

Conclusion

Family physicians are at the forefront of cancer diagnosis. Following the stepwise approach outlined will make diagnosis, staging, and referral more efficient, decreasing the diagnostic interval and improving patient care by addressing issues such as fertility, vaccinations, and smoking cessation. Timely workup of new malignancies will help preserve the patient-doctor relationship, and, if patients are referred at an earlier stage of disease, might result in improved survival.

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Competing interests
None declared

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