The impact of concordance with a lung cancer diagnosis pathway guideline on treatment access in patients with stage IV lung cancer

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Background: Timely access to treatment of lung cancer is dependent on efficient and appropriate patient assessment and early referral for diagnostic workup. This study assesses the impact of Cancer Care Ontario (CCO) Lung Cancer Diagnostic Pathway Guideline (LCDPG) concordance on access to treatment of stage IV lung cancer patients referred to the Diagnostic Assessment Program (DAP) at a Canadian tertiary cancer centre.

Methods: This retrospective cohort study includes patients diagnosed with clinical stage IV lung cancer referred to the DAP at a Canadian tertiary cancer centre between November 1, 2015 and May 31, 2017. Referral concordance was determined based on CCO LCDPG. The primary outcome; time to treatment from initial healthcare presentation; was compared between the concordant and discordant referrals.

Results: Two hundred patients were referred for clinical stage IV lung cancer during the study period. Of these referrals, 151 (75.5%) were assessed and referred in concordance with LCDPG. Guideline concordant referrals were associated with reduced time to treatment from first healthcare presentation compared with guideline discordant referrals (55.3 *vs.* 108.8 days, P<0.001). Time to diagnostic procedure (32.2 *vs.* 86.7 days, P<0.001) and decision to treat (38.5 *vs.* 93.8 days, P<0.001) were also reduced with guideline concordance. The most common reason for discordant assessment and referral was delayed or inadequate investigation of symptoms in a high risk patient (32.7% of discordant referrals).

Conclusions: Guideline concordant assessment and referral of stage IV lung cancer patients results in reduced time to diagnosis and treatment. Future research and education should focus on improving factors that delay DAP referral.

Keywords: Lung cancer; diagnostic pathway; concordance

Introduction

Lung cancer is the leading cause of cancer mortality worldwide (1). In 2016, there were 28,539 lung cancer diagnoses in Canada with 20,800 lung cancer deaths, representing a 73% mortality (2). The majority of lung cancers are diagnosed at an advanced stage which is responsible for a poor 5-year lung cancer survival (~16%) (3). In Ontario, of staged cancers (prostate, female breast, colorectal, lung and cervix), lung cancer is most likely to be diagnosed at stage III or IV (70.5% of all staged lung cancers) with stage IV cancers accounting for 49.4% of all staged lung cancers (4). Diagnosis of stage IV lung cancer is associated with poor survival and high health care utilization (5). A large proportion of Ontario patients with advanced lung cancer are hospitalized in the final 30 days of life which may reflect gaps in addressing needs of this patient population (4).

An efficient approach to the assessment and diagnosis of patients with suspected lung cancer is essential in providing prompt access to effective treatment. However, delays in this process are commonly encountered with significant heterogeneity observed across healthcare institutions (6). Such delays may be due to prolonged diagnostic work up preceding and following specialist referral (7).

In response to the need for an efficient and multidisciplinary approach to the assessment of patients with suspected lung cancer, tertiary health institutions within Ontario have established streamlined diagnostic assessment pathways (8,9). One such program was effective in reducing the time from initial suspicion of lung cancer to a diagnosis being made (8). This improvement was achieved by a multifaceted approach including a streamlined referral process and a common diagnostic algorithm.

Similarly, the University Health Network (UHN) established the Lung Rapid Assessment and Management Program (LungRAMP) in 2009. This multidisciplinary Diagnostic Assessment Program (DAP) aimed to streamline and improve access to cancer care in Ontario lung cancer patients. Between 2010 and 2017, the UHN DAP has seen a 60% increase in referrals. Overall, 2,700 patients were assessed. The majority of referred cancer patients (70%) were not surgical candidates. Advanced lung cancer has a negative impact on patient's quality of life (QOL) and survival (10) and is associated with high health care-related costs (11-13). Timely access to treatment is dependent on efficient and appropriate patient assessment and early referral for diagnostic workup. The UHN DAP has a 21-day target from receiving a patient referral to a decision to treat, which has been based on the expert consensus within Cancer Care Ontario (CCO) with a goal to have at least 50% of patients referred to any lung cancer DAP, meet this arbitrary target (14).

In November of 2015 a multidisciplinary expert panel assembled by the CCO updated the existing Lung Cancer Pathway Map, to serve as an evidence-based best practice guide to diagnostic assessment of patients with suspected and known lung cancer (15). This utility of this new Lung Cancer Diagnostic Pathway Guideline (LCDPG) in improving patient access to prompt diagnosis and treatment has not previously been assessed in clinical practice.

This study aims to assess the impact of referral concordance with a new LCDPG on access to treatment in patients with stage IV lung cancer. It also aims to assess the efficiency of a DAP in providing a diagnosis and access to treatment in patients with stage IV lung cancer. We present the following article in accordance with the STROBE reporting checklist.

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization. Ethics approval for this study was granted by the Research Ethics Board (REB) at the UHN. A single center retrospective cohort study was conducted of adult patients referred to the UHN DAP with a clinical stage IV lung cancer between November 1, 2015 and May 31, 2017. Lung cancer staging was based on the 7th edition of the TNM staging system (16). Existing medical records were retrospectively analyzed. These included province wide electronic medical records (Connecting Ontario), the UHN electronic patient record (EPR) and archived patient referral documents.

Patients were excluded if they received a diagnosis of malignancy other than lung cancer or if a definitive tissue diagnosis was not reached. Patients were also excluded if clinical stage at the time of diagnosis was not stage IV. Patients meeting the inclusion criteria were divided into two groups: (I) patients referred in concordance with the CCO LCDPG; (II) patients referred in discordance with the CCO LCDPG. Initial healthcare assessment and referral was deemed discordant according to the following categories: (I) inadequate initial investigation of suspicious symptoms as per CCO LCDPGs (15); (II) incorrect follow-
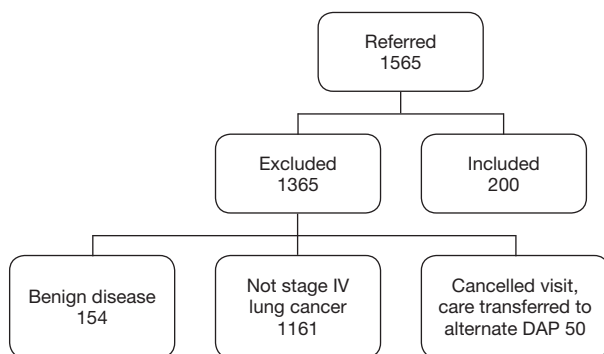
Figure 1 Patient selection flowchart.

up of presumed alternative diagnosis as per CCO LCDPGs; (III) no further imaging for suspicious chest radiograph; (IV) no referral made after suspicious CT imaging as per CCO LCDPGs.

The primary study outcome was time from initial healthcare presentation to treatment initiation. Secondary outcomes were (I) time from initial healthcare presentation to diagnosis; (II) time from initial healthcare presentation to decision to treat; (III) time from referral to treatment; (IV) time from referral to diagnostic procedure; (V) time from referral to decision to treat; (VI) healthcare utilisation from referral to treatment initiation; (VII) number of diagnostic procedures required to achieve a diagnosis; and (VIII) type of diagnostic procedure used.

The initial healthcare presentation was defined as the first documented episode of the patient being assessed for signs, symptoms, or investigation findings attributable to the eventual diagnosis of lung cancer. The date of decision to treat was defined as the date on which an initial treatment modality was chosen, and/or a referral to an appropriate oncology service was made for consideration of treatment.

Statistical analysis

Descriptive statistics were summarized as either mean (± SD), 95% CI or median with corresponding Interquartile range (IQR) for continuous data (depending on its distribution), or frequencies for categorical data. Comparisons between patient groups were assessed using the Student *t*-test for continuous data, and Fisher's Exact Test for categorical data. All tests were two sided with a P value of <0.05 indicating statistical significance. Analysis was conducted using Microsoft Excel (Microsoft Office 365 ProPlus Version 15.0.4911.1002).

Results

In the time frame of the study, 1,565 patients were referred to the UHN DAP. One thousand three hundred and sixty-five patients did not meet the inclusion criteria (*Figure 1*). A total of 200 patients met the inclusion criteria and were included in the final analysis. One hundred and fifty-one (75.5%) patients were assessed and referred in concordance with the CCO guidelines. Discordant assessment and referral occurred in 49 patients (24.5%). Of these discordant referrals, the reasons for discordance included inadequate initial investigation of suspicious symptoms (32.7%), incorrect follow-up of presumed alternative diagnosis (32.7%), no further imaging for suspicious chest radiograph (24.5%), and no referral to DAP despite suspicious CT imaging (30.6%). Clinical characteristics of all patients are outlined in *Table 1*. Patient characteristics were similar in both groups however the frequency of hemoptysis was higher in patients referred discordantly (concordant 9.3% *vs.* discordant 26.6%, P=0.004). The presence of pleural effusion was also more common in discordant referrals (7.3% *vs.* 34.7%, P=0.001). Forty patients (20%) were referred to the DAP after a tissue diagnosis was made.

The impact of referral concordance with CCO guidelines on patient treatment access from first healthcare presentation is outlined in *Figure 2*. Time from first presentation to treatment was significantly shorter in patients referred in concordance with CCO guidelines compared with discordant referrals (55.3±3.1 *vs.* 108.8±5.0 days, P<0.001). Time from first presentation to diagnostic biopsy (32.2±1.8 *vs.* 86.7±6.9 days, P<0.001) and time from first presentation to decision to treat (38.4±1.9 *vs.* 93.8±6.5 days, P<0.001) were also significantly reduced when referrals were concordant with guidelines. Time from healthcare presentation to treatment was not significantly different between patients referred to the DAP with or without a tissue diagnosis (68.4±46.6 *vs.* 68.5±46.8 days, P=0.99)

The impact of referral concordance on treatment access from time of referral is displayed in *Figure 3*. There was no significant difference between concordant and discordant referrals in time from referral to diagnostic biopsy (18.5±1.2 *vs.* 22.0±2.7 days, P=0.23), decision to treat (22.9±1.3 *vs.* 24.4±2.6 days, P=0.59), or treatment initiation (39.7±2.6 *vs.* 39.4±3.3 days, P=0.95). Decision to treat was within 21 days of referral in 54.5% of all patients referred to the DAP. An average of 4.9 patient visits to hospital occurred between referral to DAP and treatment initiation. There was no significant difference observed in hospital visits between

Table 1 Patient characteristics

Characteristics	All patients, N=200 [95% CI]	Concordant referrals, N=151 [95% CI]	Discordant referrals, N=49 [95% CI]	P value
Symptoms				
Cough	116 (58.0%) [51.1–64.3]	87 (57.6%) [49.6–65.2]	29 (59.2%) [45.2–71.8]	0.88
Chest pain	39 (19.5%) [14.9–25.6]	30 (19.9%) [14.2–27.0]	9 (18.4%) [9.6–31.6]	1.00
Hemoptysis	27 (13.5%) [9.4–19.0]	14 (9.3%) [5.5–15.1]	13 (26.6%) [16.1–40.4]	0.004
Dyspnea	58 (29.0%) [23.1–35.5]	44 (29.1%) [22.5–36.9]	14 (28.6%) [17.8–42.5]	1.00
Weight loss	68 (34.0%) [27.8–40.8]	54 (35.8%) [28.6–43.7]	14 (28.6%) [17.8–42.5]	0.39
Neurological symptoms	6 (3%) [1.2–6.5]	6 (4.0%) [1.7–8.6]	0 (0.0%) [0.0–0.9]	0.34
Fatigue	23 (11.5%) [7.7–16.7]	18 (11.9%) [7.6–18.1]	5 (10.2%) [4.0–22.2]	1.00
MSK pain (non-chest)	10 (5%) [2.6–9.1]	10 (6.6%) [3.5–11.9]	0 (0.0%) [0.0–0.9]	0.12
Asymptomatic	34 (17%) [12.4–22.9]	29 (19.2%) [13.7–26.3]	5 (10.2%) [4.0–22.2]	0.19
MRC dyspnea score				
1	117 (58.5%) [51.6–65.1]	92 (60.9%) [53.0–68.4]	25 (51.0%) [37.5–64.4]	0.26
2	47 (23.5%) [18.1–29.9]	32 (21.2%) [15.4–28.4]	15 (30.6%) [19.4–44.6]	0.18
3	20 (10%) [6.6–15.0]	14 (9.3%) [5.5–15.1]	6 (12.2%) [5.4–24.6]	0.59
4	15 (7.5%) [4.5–12.0]	12 (8.0%) [4.5–13.5]	3 (6.1%) [1.5–17.2]	1.00
5	1 (0.5%) [0.0–3.1]	1 (0.7%) [0.0–4.0]	0 (0.0%) [0.0–0.9]	1.00
Comorbidities				
None	61 (30.5%) [24.5–37.2]	44 (29.1%) [22.5–36.9]	17 (34.7%) [22.9–48.7]	0.48
COPD	29 (14.5%) [10.2–20.1]	23 (15.2%) [10.3–21.9]	6 (12.2%) [5.4–24.6]	0.82
Asthma	4 (2%) [0.6–5.2]	2 (1.3%) [0.1–5.0]	2 (4.1%) [0.3–14.5]	0.25
Diabetes mellitus	35 (17.5%) [12.8–23.4]	23 (15.2%) [10.3–21.9]	12 (24.5%) [14.5–38.2]	0.19
Coronary heart disease	21 (10.5%) [6.9–15.6]	17 (11.3%) [7.1–17.4]	4 (8.2%) [2.7–19.7]	0.79
Hypertension	90 (45%) [38.3–51.9]	70 (46.4%) [38.6–54.3]	20 (40.8%) [28.2–54.8]	0.51
Venous thromboembolism	6 (3%) [1.2–6.5]	4 (2.7%) [0.8–6.8]	2 (4.1%) [0.3–14.5]	0.64
Depression	11 (5.5%) [3.0–9.7]	7 (4.6%) [2.1–9.4]	4 (8.2%) [2.7–19.7]	0.47
Referring physician				
Emergency physician	20 (10%) [6.5–15.0]	18 (11.9%) [7.6–18.1]	2 (4.1%) [0.3–14.5]	0.17
General practitioner	130 (65%) [58.2–71.3]	99 (65.6%) [57.7–72.7]	31 (63.3%) [49.2–75.4]	0.86
Respirologist	32 (16%) [11.5–21.6]	21 (13.9%) [9.2–20.4]	11 (22.4%) [12.9–36.1]	0.18
Oncologist	8 (4%) [1.9–7.8]	5 (3.3%) [1.2–7.7]	3 (6.1%) [1.5–17.2]	0.41
Thoracic surgeon	6 (3%) [1.2–6.5]	5 (3.3%) [1.2–7.7]	1 (2.0%) [0.0–11.7]	1.00
Other	4 (2%) [0.6–5.2]	3 (2.0%) [0.4–5.9]	1 (2.0%) [0.0–11.7]	1.00
Diagnosis present at time of referral	40 (20%) [15.0–26.1]	34 (22.5%) [16.6–30.0]	6 (12.2%) [5.4–24.6]	0.15

Table 1 (*continued*)

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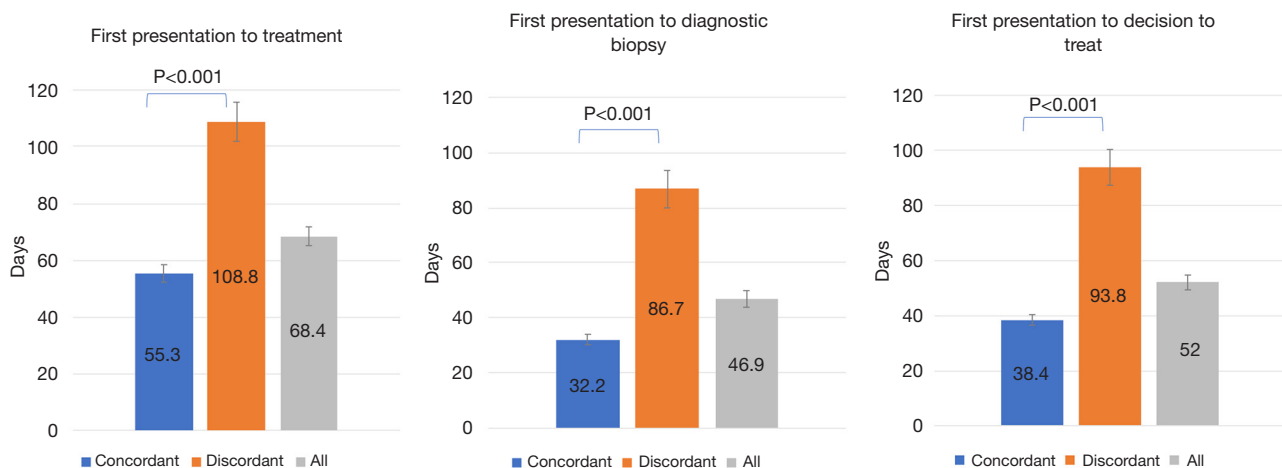| Characteristics	All patients, N=200 [95% CI]	Concordant referrals, N=151 [95% CI]	Discordant referrals, N=49 [95% CI]	P value
Pathology type				
NSCLC				
Adenocarcinoma	116 (58.5%) [51.1–64.3]	86 (57.0%) [49.0–64.6]	30 (61.2%) [47.2–73.6]	0.62
Squamous cell	33 (16.5%) [12.0–22.3]	26 (17.2%) [12.0–24.1]	7 (14.3%) [6.8–27.0]	0.83
Large cell	16 (8%) [4.9–12.7]	11 (7.3%) [4.0–12.7]	5 (10.2%) [4.0–22.2]	0.55
Poorly differentiated	3 (1.5%) [0.3–4.5]	3 (2.0%) [0.4–6.0]	0 (0.0%) [0.0–0.9]	1.00
Adenosquamous	1 (0.5%) [0.0–3.1]	1 (0.7%) [0.0–4.0]	0 (0.0%) [0.0–0.9]	1.00
Small cell carcinoma	28 (14%) [9.8–19.5]	22 (14.6%) [9.8–21.1]	6 (12.2%) [5.4–24.6]	0.82
Carcinoid	3 (1.5%) [0.3–4.5]	2 (1.3%) [0.1–5.1]	1 (2.0%) [0.0–11.7]	0.57
Targetable mutation present	72 (36%) [29.6–42.9]	61 (40.4%) [30.8–45.6]	11 (22.4%) [12.9–36.0]	0.18
TNM stage (8th edition)				
M1a	66 (33%) [26.9–39.8]	47 (31.1%) [24.3–38.9]	19 (38.8%) [26.4–52.8]	0.38
M1b	134 (67%) [60.0–73.5]	104 (68.9%) [60.8–76.2]	30 (61.2%) [46.2–74.8]	0.38
Pleural effusion present	28 (14%) [9.8–19.4]	11 (7.3%) [4.0–12.7]	17 (34.7%) [22.9–48.7]	0.001
Initial treatment modality				
None	26 (13%) [9.0–18.4]	22 (14.6%) [9.8–21.1]	4 (8.2%) [2.7–19.7]	0.33
Chemotherapy	86 (43%) [36.3–50.0]	69 (45.7%) [37.6–53.7]	17 (34.7%) [22.9–48.7]	0.19
Radiotherapy	121 (60.5%) [53.6–67.0]	92 (60.9%) [53.0–68.4]	29 (59.2%) [45.2–71.8]	0.87
Targeted therapy	43 (21.5%) [16.4–27.7]	30 (19.9%) [14.2–27.0]	13 (26.4%) [16.1–40.4]	0.32

Figure 2 Impact of referral concordance on treatment access from first healthcare presentation.
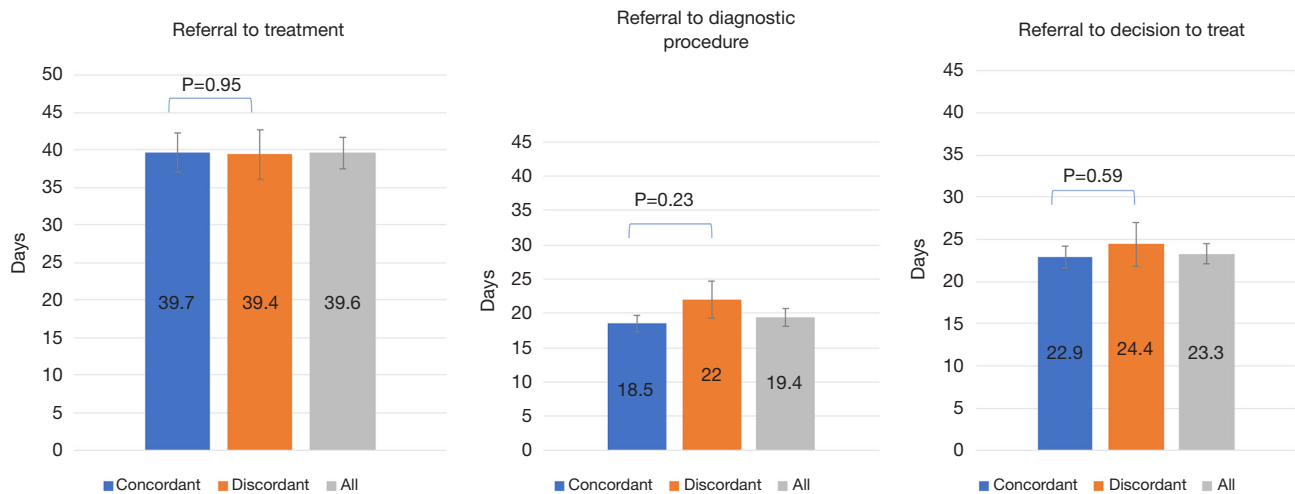
Figure 3 Impact of referral concordance on treatment access from time of referral.

Table 2 Diagnostic practices in patients with clinical stage IV lung cancer

Variable	All patients, N=200 [95% CI]	Concordant referrals, N=151 [95% CI]	Discordant referrals, N=49 [95% CI]	P value
Number or procedures required for diagnosis				
1	182 (91.0%) [86.1–94.3]	139 (92.1%) [86.5–95.5]	43 (87.8%) [75.4–94.6]	0.39
2	15 (7.5%) [4.5–12.1]	10 (6.6%) [3.5–11.9]	5 (10.2%) [4.0–22.2]	0.53
3	3 (1.5%) [0.3–4.5]	2 (1.3%) [0.1–5.0]	1 (2.0%) [0.0–11.7]	0.57
Procedure location				
Endoscopy suite	98 (49.0%) [42.2–55.9]	75 (49.7%) [41.8–57.6]	23 (46.9%) [33.7–60.6]	0.75
Interventional radiology	64 (32.0%) [25.9–38.8]	48 (31.8%) [24.9–39.6]	16 (32.7%) [21.2–46.7]	1.00
Outpatient clinic	37 (18.5%) [13.7–24.5]	27 (17.9%) [12.5–24.8]	10 (20.4%) [11.3–33.8]	0.68
Operating room	1 (0.5%) [0.0–3.1]	1 (0.7%) [0.0–4.0]	0 (0.0%) [0.0–8.7]	1.00

concordant and discordant referrals.

Diagnostic practices in patients referred with stage IV lung cancer are outlined in *Table 2*. Ninety one percent of patients referred required only one diagnostic procedure. There was no difference observed between concordant and discordant referrals in the number of diagnostic procedures required. The most common diagnostic procedure used was endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) 33.5% (95% CI, 27.3–40.3) (*Figure 4*). The most common location for performing diagnostic procedures was the endoscopy suite [49.0% (95% CI, 42.2–55.9)].

Discussion

Lung cancer is associated with significant morbidity and mortality with the majority of patients presenting with advanced disease (3). Prompt diagnostic assessment is essential to enable timely access to appropriate treatment modalities (14). The revised CCO LCDPG provides a framework to guide initial patient assessment and referral to a DAP for ongoing management (15). Our study confirms that concordance with this pathway in referring patients to a DAP reduces time to treatment access. Specifically, initial guideline concordant assessment and subsequent
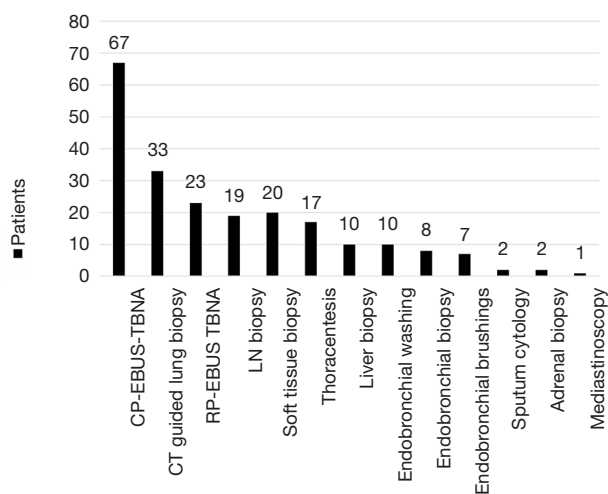
Figure 4 Diagnostic procedure used in patients referred with stage IV lung cancer.

DAP referral was associated with reduced time from initial healthcare presentation to treatment compared with discordant referrals. Time from initial healthcare presentation to diagnosis and decision to treat were also reduced with guideline concordance.

Despite the delay in accessing treatment seen in patients assessed and referred in a discordant manner, it is encouraging that the majority of patients (75.5%) were referred in concordance with the guidelines. There was no difference observed in the referral practices of General Practitioners and Specialist Physicians with regards to the CCO guidelines with similar levels of concordance seen. The specific reason for guideline discordance was varied amongst patients. The most common issue that resulted in discordant initial assessment was inadequate investigation of suspicious symptoms in a high-risk patient as defined by the CCO guidelines (see Supplementary). The most frequently encountered example of this was an unexplained cough for greater than 3 weeks that was not investigated with a chest X-ray as recommended by these guidelines. Other issues were also encountered to a similar degree, including suspicious chest radiographs or CT imaging not being further investigated or referred to the DAP as per CCO guidelines. More than one reason for discordance was also seen in some patients.

Pleural effusions and hemoptysis were more frequently observed in patients initially assessed and referred discordantly. The exact reason for this difference is not completely clear. It is possible that the delay in referral

of these patients may have resulted in further disease progression leading to these findings. However, this conclusion can only be made based on the assumption that the majority of patients initially presented to a healthcare provider with similar levels of disease burden which cannot be known from this study. Alternatively, it is possible that these findings might have been originally attributed to other medical issues (i.e., bronchitis or pneumonia for patient presenting with hemoptysis) and managed accordingly, before considering a possibility of lung cancer and pursuing appropriate lung cancer DAP referral. It is important however to reinforce that prompt patient referral and diagnosis enables timely access to treatment which may potentially reduce the frequency of such disease manifestations that impact morbidity, mortality, and healthcare utilization (5). Further studies are needed to test this hypothesis.

Time from patient referral to treatment initiation was not influenced by concordance with referral guidelines. This outcome was expected as the impact of discordance with initial assessment and referral guidelines is observed in the time period prior to a DAP referral being made. As such, the delay in access to treatment is accounted for by a delay in the time from initial healthcare presentation to the time of referral. Therefore, once a referral was received by the DAP, all patients appear to have been assessed and managed by the DAP in a similar manner resulting in no significant differences in access to treatment.

Our study supports the hypothesis that a streamlined diagnostic assessment pathway is effective in providing prompt treatment access to patients with stage IV lung cancer (6,7). Overall, a decision to treat was made within 21 days from the time of referral in 54.5% of patients, satisfying the arbitrary CCO target of 50%. Adequate tissue was obtained with a single diagnostic procedure in the vast majority of patients (91.0%). Approximately half of the diagnostic procedures completed were performed in the endoscopy suite via bronchoscopy with EBUS-TBNA being the most common method used. It is important to note however that a significant number of patients were able to undergo a diagnostic procedure in an outpatient clinic setting. This included performing diagnostic thoracentesis, peripheral lymph node biopsy, soft tissue biopsy, and sputum sampling. The use of these diagnostic techniques has multiple advantages. Firstly, the risk of complication is generally lower when performing these procedures compared with endoscopic or surgical procedures which require general anesthesia or deep

sedation (17,18). Radiology guided procedures also may carry a higher risk of complication such as pneumothorax from percutaneous lung biopsy (19). Time to diagnosis can also be reduced by performing diagnostic procedures in the outpatient clinic setting at the time of the original consultation by eliminating the need for an alternative procedure that requires a subsequent hospital visit at a later date. Finally, healthcare cost can be reduced by performing procedures in the outpatient setting that require less hospital resources (20,21). Over the years our DAP has focused on streamlining the diagnostic assessment of patients with thoracic malignancy with focus on ambulatory care. With opening of the Interventional Thoracic Surgery Suite (ITSS), many of the diagnostic procedures required in patients with lung cancer performed routinely in the operating room, have been transferred to the ambulatory setting. This resulted in a reduced health care utilization and costs without compromise to diagnostic yield (20,21).

CCO guidelines recommend a 21-day target for a treatment decision to be made in all patients referred with a new diagnosis of lung cancer. These consensus guidelines were based on recommendations from the Canadian Society of Surgical Oncology and the CCO expert consensus. This decision to treat target is based primarily on evidence relating to patients with lung cancer potentially curable with either surgery or radiotherapy (22,23). As such, the predominant concern affecting wait times in these patients is the rate of tumor growth and development of metastasis which may result in the development of more advanced or incurable disease (24,25). In patients with incurable stage IV disease at the time of referral, reasons for prompt treatment may differ. For example, patients with advanced stage lung cancer are more likely to present with significant symptoms than patients with more limited disease who may be asymptomatic (25). As a result, initiation of treatment in advanced stage lung cancer may be required more urgently for symptom palliation, particularly in cases of severe or life-threatening symptoms such as hemoptysis, spinal cord compression, or superior vena cava obstruction (25). Therefore, consideration should be made as to whether the existing CCO guidelines regarding decision to treat and treatment initiation targets for lung cancer should be stratified according to stage and symptom burden. Healthcare utilization may also differ between patients with stage IV lung cancer and less advanced disease, during the initial assessment period. Our study did not directly assess this and as such further research regarding this possibility may be warranted.

The majority of patients (80%) were referred to the DAP without a tissue diagnosis. Of significance, in patients where a tissue diagnosis was made prior to referral, the time to treatment was not significantly shorter than those patients referred without a tissue diagnosis. Therefore, despite the perceived advantage of making a diagnosis prior to DAP referral, access to treatment is not improved as a result. The reasons for this are unclear. Potentially this may represent the need for such patients to still undergo further investigations to complete staging (to confirm the suspected stage IV disease) that may have not been done prior to referral. These investigations may be non-invasive such as FDG-PET imaging or may be invasive to confirm the presence of distant disease by direct tissue sampling. As such, some patients may require further invasive diagnostic procedures despite a diagnosis of lung cancer being made prior to referral. Therefore, we would suggest that patients with a suspected clinical stage IV lung cancer be referred to a DAP to both streamline assessment and limit invasive diagnostic procedures to a minimum.

While non-invasive investigations are an important component of the diagnostic and staging algorithm of lung cancer, invasive diagnostic procedures are still required in the majority of patients to guide management decisions. This requirement has traditionally exposed patients to procedures associated with significant morbidity and healthcare burden (26). However, in recent years, minimally invasive procedures are increasingly becoming the standard of care (27). EBUS-TBNA is one such example of a minimally invasive technique that enables high diagnostic accuracy while reducing complications and morbidity associated with more traditional methods such as mediastinoscopy (28-31). The development of newer targeted therapies for lung cancer has resulted in the need to perform adequate subtyping and molecular testing on diagnostic specimens. Updated molecular testing guidelines for the selection of lung cancer patients for treatment with novel targeted therapies now recommend an extensive panel of ancillary testing to be performed on diagnostic material (32). Again, minimally invasive techniques such as EBUS-TBNA have been shown to be adequate in obtaining sufficient material for this assessment (33-37). In this study, 36% of patients with stage IV lung cancer were found to have an activating mutation or molecular characteristic potentially suitable for novel targeted therapies. As a result, 21.5% of patients were commenced on targeted therapy as their initial treatment. Importantly, in those patients found to have a targetable mutation, the vast

majority (93.1%) were able to be identified with a single diagnostic procedure. It is also noteworthy that cytology specimens from minimally invasive techniques performed in the endoscopy suite and outpatient clinic were used for the majority of patients who had a targetable mutation identified.

Our study has several limitations which predominantly relate to its retrospective design. Methodology relied on existing electronic and paper medical records. Specifically, the date of initial healthcare presentation for each patient was determined from archived referrals, physician reports, and electronic records which may have not encompassed earlier presentations to a healthcare provider. Similarly, defining referral concordance was based on retrospective records. Also, although all patient visits in our institution were able to be readily analyzed, encounters with external healthcare providers in the community and in other medical facilities may not have been documented in the online systems available for review. This may have affected our data assessing the number of healthcare visits between DAP referral and treatment initiation which did not differ between discordant and concordant referrals. Despite this, we believe these factors did not significantly affect the validity of our data and primary outcome as each patient group would be equally affected by these limitations.

In conclusion, concordance with a lung cancer diagnostic assessment pathway guideline improves access to treatment in patients with stage IV lung cancer. This study also demonstrates that a lung cancer DAP is effective in providing a streamlined pathway to prompt diagnosis and treatment. The use of such guidelines and DAPs should be promoted and used to guide the assessment and referral patients with advanced lung cancer. Future research and education should focus on improving factors that delay DAP referral.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-157). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization. Ethics approval for this study was granted by the Research Ethics Board (REB) at the University Health Network (UHN) (CAPCR ID: 17-5642.2). As this was a retrospective cohort study, not involving human experiments, waiver of consent was approved.

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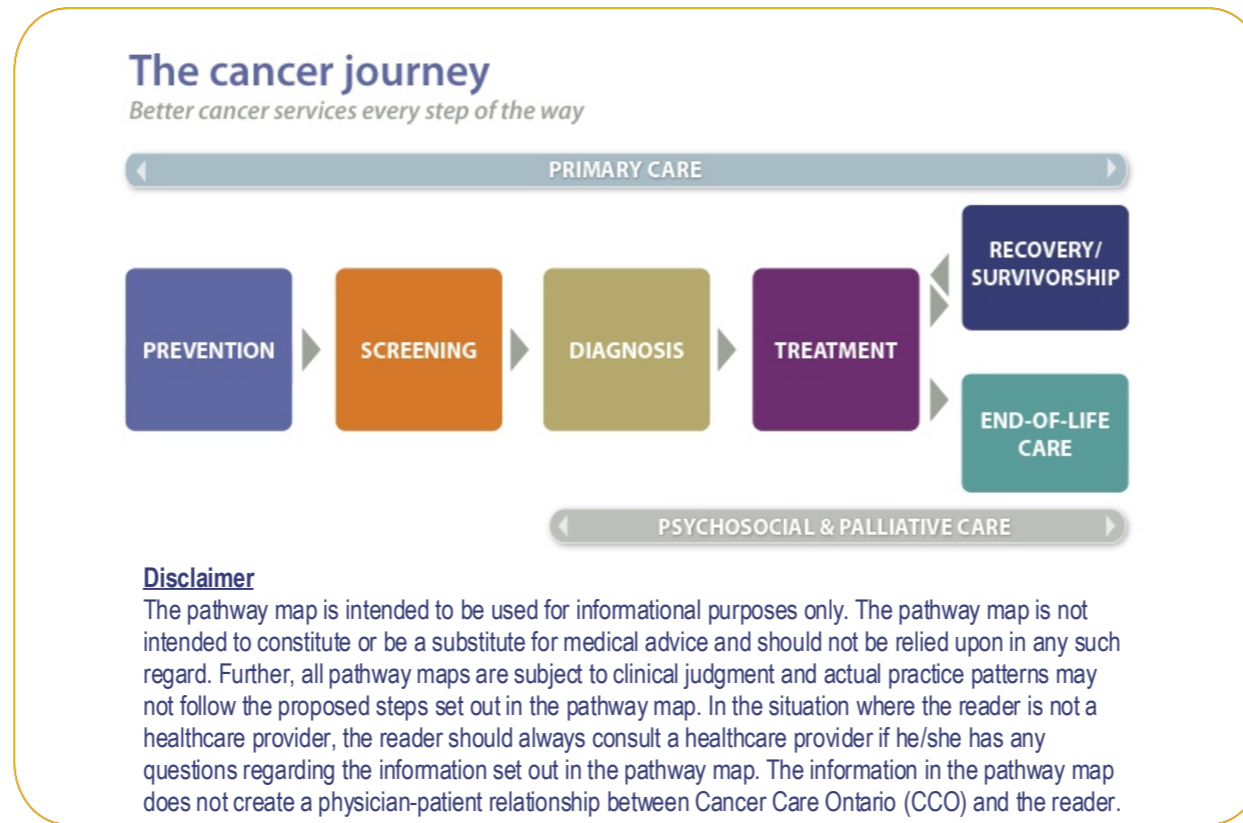
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CCO Cancer Care Ontario

Lung Cancer Diagnosis Pathway Map
Version 2015.11

The cancer journey
Better cancer services every step of the way

PRIMARY CARE

PREVENTION → SCREENING → DIAGNOSIS → TREATMENT → RECOVERY/ SURVIVORSHIP

END-OF-LIFE CARE

PSYCHOSOCIAL & PALLIATIVE CARE

Ontario
Cancer Care Ontario

Target Population

Patients who present with signs or symptoms suspicious of lung cancer.

Pathway Map Considerations

- Primary care providers play an important role in the cancer journey and should be informed of relevant tests and consultations. Ongoing care with a primary care provider is assumed to be part of the pathway. For patients who do not have a primary care provider, **Health Care Connect,** is a government resource that helps patients find a family doctor or nurse practitioner.
- Throughout the pathway map, a shared decision-making model should be implemented to enable and encourage patients to play an active role in the management of their care. For more information see **Person-Centered Care Guideline** and **EBS #19-2 Provider-Patient Communication***
- Hyperlinks are used throughout the pathway map to provide information about relevant CCO tools, resources and guidance documents.
- The term 'health care provider', used throughout the pathway map, includes primary care providers and specialists, nurse practitioners, and emergency physicians.
- For more information on the Diagnostic Assessment Program (DAP) refer to the **Organizational Standards for DAPs**

* **Note.** EBS #19-2 is older than 3 years and is currently listed as 'For Education and Information Purposes'. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

Pathway Map Legend

Colour Guide

- Primary Care
- Supportive and End of Life Care
- Pathology
- Diagnostic Assessment Program (DAP)
- Surgery
- Radiation Oncology
- Medical Oncology
- Radiology
- Multidisciplinary Cancer Conference (MCC)
- Respirologist

Shape Guide

- Intervention
- Decision or assessment point
- Patient (disease) characteristics
- Consultation with specialist
- Exit pathway
- X or X Off-page reference
- Patient path
- R Referral
- W Wait time indicator time point

Line Guide

———— Required

- - - - - - Possible

Pathway Map Disclaimer

This pathway map is a resource that provides an overview of the treatment that an individual in the Ontario cancer system may receive.

The pathway map is intended to be used for informational purposes only. The pathway map is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. Further, all pathway maps are subject to clinical judgment and actual practice patterns may not follow the proposed steps set out in the pathway map. In the situation where the reader is not a healthcare provider, the reader should always consult a healthcare provider if he/she has any questions regarding the information set out in the pathway map. The information in the pathway map does not create a physician-patient relationship between Cancer Care Ontario (CCO) and the reader.

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Patient presenting with any of the following signs suspicious for cancer:
- Hemoptysis (single episode)
- New finger clubbing
- Suspicious lymphadenopathy (e.g. cervical, supraclavicular)
- Dysphagia
- Features of metastatic lung cancer (e.g. weight loss >5 kg, focal skeletal pain, headaches)[1]
- Features suggestive of paraneoplastic syndromes[1]

Or

Patient presents with any of the following unexplained symptoms for > 3 weeks (or sooner if patient has known risk factors)[2]:
- Cough
- Anorexia
- Dyspnea
- Chest and/or shoulder pain
- Abnormal chest sounds
- Hoarseness

EBS #24-2

Underlying chronic respiratory problems presenting with unexplained changes in existing symptoms

EBS #24-2

Visit to Health Care Provider

Patient presenting with any of the following:
- Stridor
- Massive hemoptysis
- New neurological signs suggestive of brain metastases or spinal cord compression including seizure

EBS #24-2

Patient presenting with any of the following:
- Persistent non-massive hemoptysis (Multiple episodes of coughing blood or blood-streaked sputum)
- Superior vena cava syndrome/obstruction[3]

EBS #24-2

Patient presenting with abnormal imaging that reports suspicion of lung cancer (e.g. x-ray)

EBS #24-2; EBS #15-10

Chest x-ray
ES #25-1-2

Proceed to page 4 — A

Visit to emergency department
These are emergency situations and the patient should be seen in the ER (if not presenting there) and referred emergently to specialist

Imaging as appropriate

Treatment for presenting symptoms

Lung cancer suspected?
- No → **Follow-up with family physician**
- Yes → R[4]

R[4]

Proceed to Page 4 — B

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[1] Refer to the American College of Chest Physicians Clinical Practice Guideline, *Chest*, 132, 149-160 for features of a standardized evaluation for systematic metastases and a list of paraneoplastic syndromes associated with lung cancer.

[2] The following factors have been shown to increase the risk of lung cancer: current or previous smoker or second-hand exposure to tobacco smoke, history of chronic obstructive pulmonary disease, previous exposure to asbestos or other known carcinogens (e.g. radon, chromium, nickel), occupational exposure to dust or other microscopic particles (e.g. wood dust, silica), personal or family history of cancer (especially lung, head & neck), silicosis, tuberculosis

[3] These patients should be accepted by the lung DAP if the lung DAP can facilitate a diagnosis within one week.

[4] An abnormal chest x-ray or an abnormal CT scan of chest suspicious of lung cancer is required with each DAP referral. A CT scan of the chest is not required for acceptance of a lung DAP referral if the chest x-ray is abnormal but a CT scan-chest is required prior to assessment at a lung DAP. Patient history should be mandatory as part of the referral and include, at a minimum: comorbidities, medications, allergies major health issues and symptoms that prompted the DAP referral.

Lung Cancer Diagnosis Pathway Map

The pathway map is intended to be used for informational purposes only. The pathway map is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. Further, all pathway maps are subject to clinical judgment and actual practice patterns may not follow the proposed steps set out in the pathway map. In the situation where the reader is not a healthcare provider, the reader should always consult a healthcare provider if he/she has any questions regarding the information set out in the pathway map. The information in the pathway map does not create a physician-patient relationship between Cancer Care Ontario (CCO) and the reader.

B From Page 3

A From Page 3 → Results

Consolidation or unexplained pleural effusion → **Treatment as appropriate** → **Follow-up chest x-ray** EBS #24-2 → Results →
- Resolved → Follow-up with family physician
- Non-resolving EBS #24-2

High suspicion of lung cancer (based on imaging and/or clinical judgement)

R⁴

CT chest & upper abdomen Cancer Imaging Guidelines → Results →
- Suspected cancer → **DAP** Or **Specialist** Thoracic surgeon, respirologist or other as appropriate → **Begin staging tests at presentation to avoid delay at the staging phase.** Tests may include: additional CT scan, bone scan, PET scan, MRI or CT of brain (see page 7 for more detail)
- Normal imaging results → Follow-up with family physician

Staging outcomes:
- New or growing solitary peripheral mass or suspicious pulmonary nodule(s) without mediastinal or hilar lymphadenopathy → **C** Proceed to Page 5
- Central mass or clinical N1, N2, N3 → **D** Proceed to Page 5
- Pleural effusion → **E** Proceed to Page 6
- Suspected stage IV Based on scans and/or patient history → **F** Proceed to Page 6

Low suspicion of lung cancer (based on imaging and/or clinical judgement)
- **Suspected pneumonia** → **Treatment with antibiotics (1 cycle)** → **Chest x-ray** Within one month after starting treatment → Status →
  - Not resolved and suspected lung cancer
  - Not resolved and lung cancer not suspected → **Repeat chest x-ray** / Sputum culture → Results → Abnormal / Normal → Follow-up with family physician
  - Resolved
- **Suspected other infectious disease process** (e.g. tuberculosis, atypical infections) → R → **Respirologist (or Tuberculosis Specialist)** → Follow-up with specialist (notify public health if TB is diagnosed)
- **Suspected chronic obstructive pulmonary disease (COPD) or other benign lung disease** (e.g. sarcoidosis) → R → **Respirologist (or Internist)** → Follow-up with specialist or primary care provider
- **Other conditions** (e.g. pulmonary embolus, trauma) → **Treatment as appropriate**

⁴ An abnormal chest x-ray or an abnormal CT scan of chest suspicious of lung cancer is required with each DAP referral. A CT scan of the chest is not required for acceptance of a lung DAP referral if the chest x-ray is abnormal but a CT scan-chest is required prior to assessment at a lung DAP. Patient history should be mandatory as part of the referral and include, at a minimum: comorbidities, medications, allergies major health issues and symptoms that prompted the DAP referral.

C From Page 4

New or growing solitary peripheral mass or suspicious pulmonary nodule(s) without mediastinal or hilar lymphadenopathy

Interventional Radiology
Cancer Imaging Guidelines

Bronchoscopy not possible
Cancer Imaging Guidelines

Needle biopsy not possible

PET/CT scan
EBS #7-20 and
PET Scans Ontario

Core Biopsy   Or   Fine Needle Biopsy

Choice is based on the expertise of the radiologist and pathologist and the ability to obtain sufficient tissue for morphological diagnosis and molecular testing.
ES #25-1-1 and
Cancer Imaging Guidelines

Cytology[7]
Cell block should be obtained
And/Or
Pathology[7,8]

Results

Positive for cancer or suspicious

Negative but high level of clinical suspicion

Negative and low level of clinical suspicion

Thoracic Surgery
For diagnostic purposes

Cytology[7]
Cell block should be obtained
And/Or
Pathology[7,8]

Results

Positive for cancer

Negative for cancer

Ongoing follow-up care by family physician

Follow-up by family physician, specialist or pulmonary nodule clinic
Follow-up CT
As per Fleischner guidelines[9]

Results

Change in result
EBS #7-20

Stable

Ongoing follow-up care by family physician

G Proceed to Page 7

D From Page 4

Central mass or clinical N1, N2, N3

May be performed by surgeon or respirologist
Bronchoscopy[5]
Endobronchial ultrasound[6]

If there is CT evidence of hilar and/or mediastinal lymphadenopathy
Mediastinoscopy
Or
Endobronchial ultrasound[5]
If not previously done
Or
Interventional Radiology

Cytology[7]
Cell block should be obtained
And/Or
Pathology[7,8]

Results

Positive for cancer

Suspicious or negative but high level of clinical suspicion

Negative and low level of clinical suspicion

Repeat biopsy or other diagnostic testing
As appropriate

Thoracic Surgery
For diagnostic purposes

Cytology[7]
Cell block should be obtained
And/Or
Pathology[7,8]

Results

Positive for cancer

Negative for cancer

Follow-up with family physician

Follow-up by specialist

Results

Change in result
EBS #7-20

Stable for 2 years

Ongoing follow-up care by family physician

H Proceed to Page 7

[5] Depending on local resources, radial miniprobe navigational bronchoscopy with lung biopsy may be considered.

[6] If the endobronchial ultrasound transbronchial needle aspiration is negative but there is a high level of suspicion of lung cancer, a mediastinoscopy should be completed.

[7] Results go to ordering and referring physician and family physician

[8] For more information about biomarkers, refer to the Lung Cancer Tissue Pathway

[9] Follow-up as per the Fleischner guidelines. For more information see Guidelines for Management of Small Pulmonary Nodules Detected on CT Scans: A Statement from the Fleischner Society. (2005). Radiology, 237, 395-400.

E F

From page 4

Pleural effusion

Thoracentesis
Perform procedure promptly. Can be done for diagnosis or for symptom relief. Note: If malignant cells found, this condition makes the patient inoperable.
Cancer Imaging Guidelines

Tests on pleural fluid:
- Cytology (cell block should be obtained)
- Lactate dehydrogenase
- Protein concentration
- Glucose
- Amylase
- Cell count and differential
- Culture and sensitivity

Suspected stage IV
Based on scans and/or patient history

Obtain sufficient tissue sample for histological and molecular diagnosis via least invasive, most accessible and most likely to up-stage the patient
Cancer Imaging Guidelines

Cytology[7]
(cell block should be obtained)
And/Or
Pathology[7,8]

Results

Positive for cancer (Stage IV)

Suspicious or negative but high level of clinical suspicion

Repeat biopsy, thoracentesis or other diagnostic testing
As appropriate

Thoracic Surgery
For diagnostic purposes

Cytology[7]
Cell block should be obtained
And/Or
Pathology[7,8]

Results

Positive for cancer

Negative for cancer

Ongoing follow-up care by family physician

Proceed to Treatment Pathway (NSCLC page 7, 8; SCLC page 4)

Negative and low level of clinical suspicion

Follow-up by specialist

Results

Change in result
EBS #7-20

Stable

Ongoing follow-up care by family physician

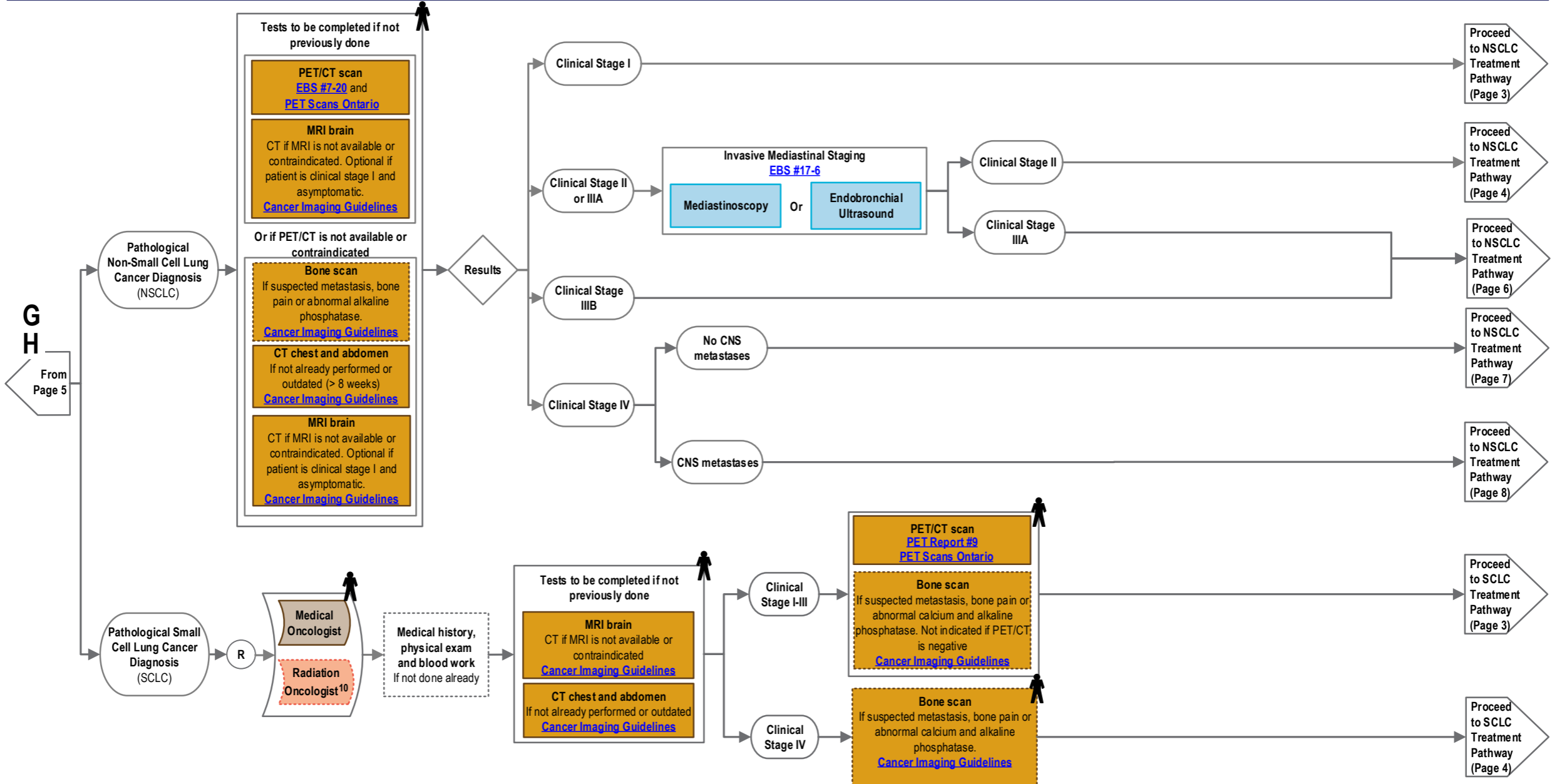[7] Results go to ordering and referring physician and family physician
[8] For more information about biomarkers, refer to the Lung Cancer Tissue Pathway
[9] Follow-up as per the Fleischner guidelines. For more information see Guidelines for Management of Small Pulmonary Nodules Detected on CT Scans: A Statement from the Fleischner Society. (2005). Radiology, 237, 395-400.

G H

From Page 5

Pathological Non-Small Cell Lung Cancer Diagnosis (NSCLC)

Tests to be completed if not previously done

- **PET/CT scan** — EBS #7-20 and PET Scans Ontario
- **MRI brain** — CT if MRI is not available or contraindicated. Optional if patient is clinical stage I and asymptomatic. Cancer Imaging Guidelines

Or if PET/CT is not available or contraindicated

- **Bone scan** — If suspected metastasis, bone pain or abnormal alkaline phosphatase. Cancer Imaging Guidelines
- **CT chest and abdomen** — If not already performed or outdated (> 8 weeks). Cancer Imaging Guidelines
- **MRI brain** — CT if MRI is not available or contraindicated. Optional if patient is clinical stage I and asymptomatic. Cancer Imaging Guidelines

→ **Results**

- **Clinical Stage I** → Proceed to NSCLC Treatment Pathway (Page 3)
- **Clinical Stage II or IIIA** → **Invasive Mediastinal Staging** EBS #17-6 (Mediastinoscopy Or Endobronchial Ultrasound) →
  - **Clinical Stage II** → Proceed to NSCLC Treatment Pathway (Page 4)
  - **Clinical Stage IIIA** → Proceed to NSCLC Treatment Pathway (Page 6)
- **Clinical Stage IIIB** → Proceed to NSCLC Treatment Pathway (Page 6)
- **Clinical Stage IV**
  - **No CNS metastases** → Proceed to NSCLC Treatment Pathway (Page 7)
  - **CNS metastases** → Proceed to NSCLC Treatment Pathway (Page 8)

Pathological Small Cell Lung Cancer Diagnosis (SCLC)

→ **R** →

- **Medical Oncologist**
- **Radiation Oncologist [10]**

→ **Medical history, physical exam and blood work** — If not done already

→ **Tests to be completed if not previously done**

- **MRI brain** — CT if MRI is not available or contraindicated. Cancer Imaging Guidelines
- **CT chest and abdomen** — If not already performed or outdated. Cancer Imaging Guidelines

→

- **Clinical Stage I-III**
  - **PET/CT scan** — PET Report #9, PET Scans Ontario
  - **Bone scan** — If suspected metastasis, bone pain or abnormal calcium and alkaline phosphatase. Not indicated if PET/CT is negative. Cancer Imaging Guidelines
  - → Proceed to SCLC Treatment Pathway (Page 3)
- **Clinical Stage IV**
  - **Bone scan** — If suspected metastasis, bone pain or abnormal calcium and alkaline phosphatase. Cancer Imaging Guidelines
  - → Proceed to SCLC Treatment Pathway (Page 4)

[10] If emergency situation, symptomatic brain metastases, superior vena cava obstruction, spinal compression or stage I-III disease.