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# Time intervals and routes to diagnosis for lung cancer in ten jurisdictions: cross-sectional study findings from the International Cancer Benchmarking Partnership (ICBP)



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**Time intervals and routes to diagnosis for lung cancer in ten jurisdictions: cross-sectional study findings from the International Cancer Benchmarking Partnership (ICBP)**

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## Abstract

### Objective

Differences in time intervals to diagnosis and treatment between jurisdictions may contribute to previously reported differences in stage at diagnosis and survival. The International Cancer Benchmarking Partnership Module 4 (ICBP M4) reports the first international comparison of routes to diagnosis and time intervals from symptom onset until treatment start for lung cancer patients.

### Design

Patients, their primary care physicians (PCP) and cancer treatment specialists (CTS) were surveyed in Victoria (Australia), Manitoba and Ontario (Canada), Northern Ireland, England, Scotland and Wales (UK), Denmark, Norway and Sweden. Using Wales as the reference jurisdiction, the 50$^{th}$, 75$^{th}$ and 90$^{th}$ percentiles for intervals were compared using quantile regression adjusted for age, gender and comorbidity.

### Participants

Consecutive newly diagnosed lung cancer patients, aged >40 years, identified through cancer registries. Of 10,203 eligible patients contacted, 2,631 (25.8%) responded and 2,143 were included in the analysis.

### Primary and secondary outcome measures:

Interval lengths (days, primary), routes to diagnosis, symptoms (secondary).

### Results

With the exception of Denmark, in all other jurisdictions the median total interval from symptom onset to treatment, for respondents diagnosed in 2012-15, was similar to that of Wales. Overall 55% (range 35-75%) were diagnosed following presentation to the PCP. Jurisdiction specific significant differences in patient, diagnostic and treatment intervals, especially for the 10% of patients who waited the longest, were observed. Based on overall trends, jurisdictions could be grouped into those with trends of reduced, longer and similar intervals to Wales. All symptoms other than persistent cough were less frequently reported by the PCP when compared to patients.

### Conclusion

There are differences between jurisdictions in interval lengths, especially for patients who wait the longest. The data will allow jurisdictions to develop more focused lung cancer policy and clinical initiatives. Future analysis will explore if these differences in intervals impact on stage or survival.

**Key words:**
lung cancer, routes to diagnosis, time intervals, international health systems, symptomatic presentation

**Strengths and limitations of this study**

- This is the first international study to use standarised survey methods and definitions to systematically examine key intervals from patients first noticing symptoms or bodily changes until the start of treatment for lung cancer
- Recall bias was minimised by the triangulation of different data sources and by patients completing the questionnaire within a limited time window (median 5 months) after the cancer diagnosis
- A key limitation, as with all questionnaire-based studies was non-response bias which varied across jurisdictions, and analyses were adjusted for age, gender and comorbidity, but not for ethnicity and education as there are different classification systems in participating countries
- Recruitment of patients up to 9 rather than 6 months after diagnosis might have magnified selection bias due to high mortality in lung cancer but a sensitivity analysis suggests that this did not impact on the results.
- In Norway and Victoria, a small sample size and restriction of eligibility to only surgical patients, respectively, means some comparisons are made with caution – this mainly applies to the treatment interval and some patient characteristics.

## Introduction

Lung cancer is the most common cancer worldwide, with nearly 1.83 million cases diagnosed in 2012, and is the leading cause of cancer death globally, accounting for 19% of cancer deaths.[1] Survival is typically low, with 5-year survival in Europe and North America <20%.[2] A key factor is diagnosis at advanced stage. Reasons for this are multi-faceted and include delays due to the atypical nature of some presenting symptoms, poor sensitivity of chest X-rays and primary care physicians not acting quickly enough.[3] Within European countries, differences of 12 and 5 percentage points in 1- and 5-year relative survival, respectively, have been reported for lung cancers diagnosed between 1999-2007.[4] This and other international comparisons raises the possibility of additional contributory factors such as variations in referral patterns, access to diagnostic tests and delays in treatment.[5]

One way of addressing this is to chart the patient journey from first noticing symptoms to treatment start. While many national studies using different methodologies have reported on time intervals to treatment in lung cancer, as far as we are aware no international comparisons exist.[6-18]

The International Cancer Benchmarking Partnership (ICBP) was established to explore differences in cancer outcomes and their causes in countries with comparable wealth and universal access to healthcare.[19] We report results from Module 4 (ICBP M4) on differences in time intervals and routes to diagnosis in symptomatic lung cancer patients from ten jurisdictions in Australia, Canada, Denmark, Norway, Sweden and the United Kingdom.

## Methods

Methods have been previously detailed.[20] In brief, in each of the ten participating jurisdictions (Victoria (Australia), Manitoba, Ontario (Canada), Denmark, Norway, Sweden Northern Ireland, England, Scotland and Wales), consecutive patients aged ≥40 years, newly diagnosed with malignant lung or bronchus cancer (ICD-10:C34.0-C34.9; behaviour code ICD-O-3) were identified by the cancer registry using validated methods (hospital episode, cancer registration, pathology). Exclusion criteria included previous lung or synchronous cancers. Patients with a previous non-lung primary cancer were eligible. Target recruitment was 200 symptomatic patients per jurisdiction.

Following a vital status check, cancer registries posted the patient questionnaire (Supplementary File 1) either 1) to the relevant primary care physician (PCP) who then forwarded the pre-addressed envelope (Wales, England, Scotland) or 2) to the patient

directly or via the research team (remaining seven jurisdictions). In an attempt to decrease attrition and recall bias, the protocol initially specified that all patient questionnaires should be completed within 6 months of diagnosis. As there were administrative delays in cancer notification, this was extended to 9 months.

On receipt of a completed patient questionnaire, in all jurisdictions except Sweden, the relevant PCP and cancer treatment specialist (CTS) were sent questionnaires (Supplementary Files 2 and 3). Specialists provided information on diagnosis and start date of treatment. The latter was collected directly from registry records in Northern Ireland and clinical databases in Denmark. Manitoba did not provide specialist data. Date of diagnosis and stage was also collected where possible through cancer registries. Information on the types of treatment (surgery, chemotherapy, radiotherapy and other) were obtained from the patient survey.

*Data handling*

Data were recoded centrally to ensure that the same explicit rules were applied throughout. Patients in whom age, date of diagnosis or consent were missing were excluded from analyses. Rules were used to combine data from the different sources in a standardised way that ensured reproducibility and transparency (Supplementary File 4). The rules employed a 'hierarchy' principle in terms of the order in which different data sources were used, and included imputation rules based on the available data. The exact rule was guided by the measure in question – for example, patient interval was collected primarily from the patient questionnaire whereas primary care time-points from the PCP questionnaire. All the measures were further validated using algorithms for outliers and implausible measures (e.g. negative time intervals).

*Routes to diagnosis and symptoms prompting physician visit*

These were derived from patient and PCP responses. Symptoms were coded by two PCP authors (DW and PV) into 'lung cancer specific' or 'other' (Supplementary File 5, Table 1).

*Time intervals*

Time intervals were derived using the checklist for the Aarhus Statement.[21] The following time-points were used to calculate the corresponding time intervals (Figure 1):

- first noticing symptoms
- first presentation to health care
- first referral to secondary care

- diagnosis date
- start of curative or palliative treatment

FIGURE 1

All time-points were validated if there were obvious inconsistency and negative intervals were set to 0 days. All intervals were truncated at 365 days. Missing data were imputed based on specific rules to ensure that the direction of a possible misclassification bias was known.

*Demographics*

Health status was measured using the self-reported general health item from short form 36 health survey (SF36).[22] Comorbidity was defined as one of four patient or PCP-reported diseases (heart or lung disease, stroke or diabetes) and categorised into: 'none', 'medium' (one or two) or 'high' (three or four). Level of educational was categorised as 'low' (vocational school or lower) and 'high' (university). Stage data (tumour, node, metastasis - TNM - classification) was grouped as I, II, III, IV or missing.[23]

*Statistical analysis*

Patient characteristics across jurisdictions were compared using Kruskal-Wallis test and Pearson's chi-squared test. Quantile regression was used to estimate differences in intervals.[24] The 50$^{th}$, 75$^{th}$ and 90$^{th}$ percentiles were compared, using Wales as the reference jurisdiction as it had the lowest lung cancer survival in ICBP Module 1 analysis.[5] Counting days, we used the 'qcount' procedure.[25, 26] Parameters were calculated with 1000 jittered samples. For all interval analyses, multivariable models controlled for differences in age, sex and comorbidity between jurisdictions. Significance level was set to $\leq$0.05 with 95% confidence intervals (95%CI) calculated where appropriate. Statistical analyses were carried out using STATA v14.

*Sensitivity and validity analyses*

All analyses were repeated using only (1) those who fulfilled the 6-month cut-off criteria for interval from diagnosis to questionnaire completion and (2) patient data. The effect of excluding patients for whom at least one interval was missing was investigated. Agreement between the different data sources (registry, patient, PCP (except in Sweden) and CTS (except in Sweden and Manitoba) was measured by Lin's concordance correlation coefficient (CCC).[27]

*Patient involvement*

The research questions for this survey drew on an extensive literature relating to diagnosis and treatment delays leading to negative patient experiences. While patient experience was not a primary outcome measure for this study, patients were given the opportunity to comment on their experience through questionnaire free-text response options (under separate analysis). Patients were involved in the piloting of study instruments to ascertain if recruitment and questionnaire content and dissemination strategies were appropriate, described elsewhere.[20] Each jurisdiction has committed to communicating the findings and local implications of this study to organisations representing their study participants.

**Results**

Of 14,583 lung cancer patients, diagnosed between October 2012 and March 2015 who were alive when identified, 70% (10,203/14,583) were contacted (Table 1). 2,631 (25.8% of contacted, 18% of eligible) completed the patient questionnaire at a median of 5 months (range: 0.1,9) after diagnosis (Table 2). The response rate of contacted patients varied from 11.1% (146/1318) in Norway to 61.8% (333/539) in Denmark. Responding patients were more likely to be aged 60-79 years with less advanced stage (Table 1) and alive one year post diagnosis (data not shown). Of the 2,631 responses, 2,143 (81.5%) were included in the analyses which equates to 14.7% (2,143/14,583) of eligible patients. The key reason respondents were excluded were local oversampling (43.9%; 214/488) for additional analyses (Table 1). In Victoria, the registry was only able to contact patients who had undergone surgery while the sample size in Norway was limited (n=88) due to delays in securing appropriate approvals.

**Table 1:** Cohort for all ten jurisdictions and overall

| Jurisdiction | Patients approached via PCP | | | | | | Patient approached directly by registries/research teams | | | | | | | | | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Wales | | England | | Scotland | | N Ireland | | Denmark | | Manitoba | | Ontario | | Sweden | | Norway | | Victoria | | | |
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| **Eligible patients** [a, b] | **1,811** | **(100)** | **2,517** | **(100)** | **1,366** | **(100)** | **620** | **(100)** | **539** | **(100)** | **980** | **(100)** | **4,080** | **(100)** | **493** | **(100)** | **1,318** | **(100)** | **859** | **(100)** | **14,583** | **(100)** |
| **Packs sent to PCP** [c, d] | **1,811** | **(99.7)** | **1,759** | **(69.9)** | **1,137** | **(83.2)** | | | | | | | | | | | | | | | **4,707** | **(82.7)** |
| pack not forwarded by PCP | 547 | (30.1) | 255 | (14.5) | 201 | (17.7) | | | | | | | | | | | | | | | 1,003 | (21.3) |
| unsure if pack forwarded by PCP | 531 | (29.2) | 559 | (31.8) | 234 | (20.6) | | | | | | | | | | | | | | | 1,324 | (28.1) |
| **Patients contacted by PCP** [c, d] | **733** | **(40.4)** | **945** | **(53.7)** | **702** | **(61.7)** | | | | | | | | | | | | | | | **2,380** | **(50.6)** |
| **Patients approached directly** [c] | | | | | | | **614** | **(99.0)** | **539** | **(100)** | **745** | **(76.0)** | **3,687** | **(90.4)** | **493** | **(100)** | **1,200** | **(91)** | **545** | **(63.4)** | **7,823** | **(88)** |
| patient died | | | | | | | 6 | (1.0) | 0 | (0.0) | 103 | (13.8) | 249 | (6.8) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 358 | (4.6) |
| no address | | | | | | | 0 | (0.0) | 0 | (0.0) | 9 | (1.2) | 255 | (6.9) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 264 | (3.4) |
| Other | | | | | | | 0 | (0.0) | 0 | (0.0) | 6 | (0.8) | 215 | (5.8) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 221 | (2.8) |
| **Patient responses (% of eligible patients)** [c] | **223** | **(12.3)** | **261** | **(10.4)** | **235** | **(17.2)** | **226** | **(36.5)** | **333** | **(61.8)** | **205** | **(20.9)** | **572** | **(14.0)** | **217** | **(44)** | **146** | **(11.1)** | **213** | **(24.8)** | **2,631** | **(18)** |
| **Patient responses (% of contacted)** [e] | **223** | **(30.4)** | **261** | **(27.6)** | **235** | **(33.5)** | **226** | **(37.2)** | **333** | **(61.8)** | **205** | **(32.7)** | **572** | **(19.3)** | **217** | **(44)** | **146** | **(12.2)** | **213** | **(39.1)** | **2,631** | **(27.5)** |
| extra sample for local purpose | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 214 | (37.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 214 | (8.1) |
| other | 0 | (0.0) | 0 | (0.0) | 35 | (14.9) | 25 | (11.1) | 38 | (11.4) | 0 | (0.0) | 43 | (7.5) | 0 | (0.0) | 0 | (0.0) | 3 | (1.4) | 144 | (5.5) |
| **Patient surveys submitted for analyses** [f] | **223** | **(100)** | **261** | **(100)** | **200** | **(85.1)** | **201** | **(88.9)** | **295** | **(88.6)** | **205** | **(100)** | **315** | **(55.1)** | **217** | **(100)** | **146** | **(100)** | **210** | **(98.6)** | **2,273** | **(86.4)** |
| excluded for analyses – total | 12 | (5.4) | 9 | (3.4) | 2 | (1.0) | 1 | (0.5) | 10 | (3.4) | 3 | (1.5) | 27 | (8.6) | 6 | (2.8) | 58 | (39.7) | 2 | (1.0) | 130 | (5.7) |
| - previous cancer | 0 | (0.0) | 5 | (1.9) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 3 | (1.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 8 | (0.4) |
| - unknown date of consent or diagnosis | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 5 | (1.7) | 0 | (0.0) | 1 | (0.3) | 6 | (2.8) | 4 | (2.7) | 0 | (0.0) | 16 | (0.7) |
| - consent too late/too early | 12 | (5.4) | 4 | (1.5) | 2 | (1.0) | 1 | (0.5) | 5 | (1.7) | 3 | (1.5) | 22 | (7.0) | 0 | (0.0) | 33 | (22.6) | 2 | (1.0) | 84 | (3.7) |
| - other | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) | 0 | (0.0) | 21 | (14.4) | 0 | (0.0 | 22 | (1.0) |
| **Patients included in analyses** [i] **(% of forwarded surveys)** | **211** | **(94.6)** | **252** | **(96.6)** | **198** | **(99.0)** | **200** | **(99.5)** | **285** | **(96.6)** | **202** | **(98.5)** | **288** | **(91.4)** | **211** | **(97.2)** | **88** | **(60.3)** | **208** | **(99.0)** | **2,143** | **(94.3)**[h] |
| **PCP surveys** [j] **(% of analysed patients)** | **133** | **(63.0)** | **196** | **(77.8)** | **149** | **(75.3)** | **181** | **(90.5)** | **218** | **(76.5)** | **109** | **(54.0)** | **93** | **(32.5)** | **n/a** [h] | | **27** | **(30.7)** | **105** | **(50.5)** | **1,211** | **(56.6)**[i] |
| **Specialist surveys** [k] **(% of analysed patients)** | **98** | **(46.4)** | **153** | **(60.7)** | **106** | **(53.5)** | **n/a** [g] | | **149** [g] | **(52.3)** | **n/a** [h] | | **62** | **(21.7)** | **n/a** [h] | | **20** | **(22.7)** | **55** | **(26.4)** | **643** | **(37.0)**[m] |

[a]Eligible as per protocol: individual aged 40 years or more, with cancer of the lung or bronchus (ICD-10 code: C34.0-C34.9; behaviour code ICD-O 3) but no synchronous primary cancer or prior history of lung cancer, alive at identification who completed consent to participate within nine months of diagnosis. [b]In some jurisdictions some 'eligible' patients had pre-opted out from being contacted and a small number where PCP information was not available. [c]Percentages of eligible patients. [d]Maximum of potentially contacted patients. i.e. sum of packs forwarded by PCP and packs unsure if forwarded by PCP. [e]Percentages of patients contacted by PCP (see note d) for Wales, England and Scotland or percentages of patients contacted directly by a registry excl. non-accessible patients (all other jurisdictions). [f] Percentages of patient responses. [g] Data obtained from registries instead in N Ireland and Denmark. [h] Data not collected in this jurisdiction. [i] Denominator = total number of forwarded cases excl. patients not included in analytic sample in Ontario. [j] Denominator r = total number of analysed cases excl. patients from Sweden. [k] Denominator = total number of analysed cases excl. patients from Sweden. Manitoba & N Ireland.

*Baseline characteristics*

The characteristics are detailed in Table 2. The cohort was predominantly White (95%), median age 70 years (IQR 64,75) with 82% reporting 'low' levels of education. Norway provided stage data classified as local, regional and distant which could not be converted to TNM stage data.

Ontario was the only jurisdiction with more female (65%) than male respondents. While self-reported health differed significantly, with Welsh patients (9%) reporting twice as high 'poor health' rates than English or Swedish (4%) and eight-fold that of Manitoba (2%), there was no difference in self-reported comorbidity rates. Even after the exclusion of Victoria, there was significant variation in early Stage (I/II) disease which ranged from 25% (Wales) to 59% (Ontario) and surgical resection rates which varied from 27% (Wales) to 58% (Ontario) (Table 2).

**Table 2.** The characteristics of eligible patients by jurisdictions and overall

| | Wales (N=211) | England (N=252) | Scotland (N=198) | N Ireland (N=200) | Denmark (N=285) | Manitoba (N=202) | Ontario (N=288) | Sweden (N=211) | Norway (N=88) | Victoria (N=208) | Overall (N=2143) | p-value[6] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Date of diagnosis of first patient | 03/04/2013 | 28/01/2013 | 26/04/2013 | 22/01/2013 | 16/05/2013 | 10/10/2012 | 08/10/2013 | 01/10/2013 | 16/01/2014 | 08/01/2013 | 10/10/2012 | |
| Date of diagnosis of last patient | 25/09/2014 | 14/08/2013 | 04/12/2013 | 02/12/2014 | 13/11/2013 | 27/03/2015 | 01/10/2014 | 30/05/2014 | 21/01/2015 | 28/12/2014 | 27/03/2015 | |
| Interval from diagnosis date of first patient to last patient in months (recruitment period) | 18 | 7 | 7 | 23 | 6 | 30 | 12 | 8 | 12 | 24 | 30 | |
| Median (range) interval diagnosis to questionnaire completion in months | 5 (0.6,9) | 5 (3,9) | 5 (1,9) | 4 (0.1,9) | 5 (2,8) | 6 (4,9) | 6 (4,9) | 4 (3,8) | 7 (5,9) | 5 (0.2,8) | 5 (0.1,9) | |
| **Age** years Median (IQR) | 71 (65, 77) | 71 (65, 77) | 70 (64, 76) | 69 (62, 75) | 70 (63, 74) | 70 (63, 77) | 70 (64, 75) | 70 (63, 75) | 69 (64, 73) | 68 (63, 73) | 70 (64, 75) | 0.010[1] |
| **Sex** n(%) Male | 127(60) | 134(53) | 100(51) | 105(53) | 151(53) | 100(50) | 131(45) | 111(53) | 46(52) | 112(54) | 1117(52) | 0.159[2] |
| **Health State** n(%) Good | 135(64) | 176(70) | 131(66) | 126(63) | 190(67) | 156(77) | 220(76) | 152(72) | 50(57) | 163(78) | 1499(70) | <0.001*[1] <0.001**[2] |
| Fair | 55(26) | 59(23) | 52(26) | 51(26) | 62(22) | 41(20) | 47(16) | 49(23) | 32(36) | 33(16) | 481(22) | |
| Poor | 20(9) | 11(4) | 14(7) | 16(8) | 18(6) | 4(2) | 16(6) | 9(4) | 6(7) | 10(5) | 124(6) | |
| Missing | 1(0.5) | 6(2) | 1(0,5) | 7(4) | 15(5) | 1(0.5) | 5(2) | 1(0.5) | 0(0) | 2(1) | 39(2) | |
| **Comorbidity**[3] n(%) No | 92(44) | 113(45) | 98(49) | 82(41) | 111(39) | 101(50) | 136(47) | 114(54) | 35(40) | 98(47) | 980(46) | 0.029*[1] 0.032**[2] |
| Medium | 111(53) | 129(51) | 92(46) | 103(52) | 157(55) | 93(46) | 132(46) | 87(41) | 48(55) | 100(48) | 1052(49) | |
| High | 7(3) | 9(4) | 8(4) | 15(8) | 11(4) | 6(3) | 18(6) | 6(3) | 5(6) | 8(4) | 93(4) | |
| Missing | 1(0.5) | 1(0.4) | 0(0) | 0(0) | 6(2) | 2(1) | 2(0.7) | 4(2) | 0(0) | 2(1) | 18(0.8) | |
| **Education** n(%) Low | 172(82) | 217(86) | 174(88) | 166(83) | 232(81) | 170(84) | 224(78) | 159(75) | 65(74) | 181(87) | 1760(82) | <0.001*[1] <0.001**[2] |
| High | 11(5) | 15(6) | 11(6) | 17(9) | 15(5) | 21(10) | 55(19) | 48(23) | 14(16) | 24(12) | 231(11) | |
| Missing | 28(13) | 20(8) | 13(7) | 17(9) | 38(13) | 11(5) | 9(3) | 4(2) | 9(10) | 3(1) | 152(7) | |
| **Ethnicity** n(%) | 205(97) | 249(99) | 197(99) | 196(98) | 267(94) | 173(86) | 261(91) | n/a | 87(99) | 199(96) | 1834(95) | |

| | Wales (N=211) | England (N=252) | Scotland (N=198) | N Ireland (N=200) | Denmark (N=285) | Manitoba (N=202) | Ontario (N=288) | Sweden (N=211) | Norway (N=88) | Victoria (N=208) | Overall (N=2143) | p-value[6] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| White | | | | | | | | | | | | <0.001*[2] <0.001**[2] |
| Asian | 1(0.5) | 0(0) | 1(0.5) | 0(0) | 0(0) | 12(6) | 21(7) | n/a | 1(1) | 6(3) | 41(2) | |
| Black | 0(0) | 1(0.4) | 0(0) | 0(0) | 1(0.4) | 0(0) | 1(0.3) | n/a | 0(0) | 0(0) | 3(0.2) | |
| Other | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 15(7) | 2(0.7) | n/a | 0(0) | 0(0) | 17(0.9) | |
| Missing | 5(2) | 2(0.8) | 0(0) | 4(2) | 17(6) | 2(1) | 3(1) | n/a | 0(0) | 3(1) | 36(2) | |
| **Smoking** n(%) Never | 13(6) | 18(7) | 12(6) | 19(10) | 15(5) | 22(11) | 31(11) | 41(19) | 11(13) | 33(16) | 215(10) | <0.001*[2] <0.001**[2] |
| Currently | 19(9) | 28811) | 26(13) | 41(21) | 58(20) | 24(12) | 29(10) | 29(14) | 11(13) | 9(4) | 274(13) | |
| In the past | 174(82) | 204(81) | 160(81) | 137(69) | 205(72) | 156(77) | 225(78) | 139(66) | 66(75) | 165(79) | 1631(76) | |
| Missing | 5(2) | 2(0.8) | 0(0) | 3(2) | 7(2) | 0(0) | 3(1) | 2(0.9) | 0(0) | 1(0.5) | 23(1) | |
| **Tumour stage – TNM** n(%) I | 26(12) | 68(27) | 49(25) | 42(21) | 74(26) | 83(41) | 133(46) | 59(28) | 3(3) | 124(60) | 661(31) | <0.001*[2] <0.001**[2] |
| II | 27(13) | 36(14) | 32(16) | 33(17) | 26(9) | 19(9) | 38(13) | 11(5) | 5(6) | 47(23) | 274(13) | |
| III | 64(30) | 57(23) | 56(28) | 59(30) | 84(29) | 48(24) | 54(19) | 40(19) | 5(6) | 19(9) | 486(23) | |
| IV | 62(29) | 80(32) | 50(25) | 62(31) | 94(33) | 48(24) | 54(19) | 94(45) | 3(3) | 13(6) | 560(26) | |
| Missing | 32(15) | 11(4) | 11(6) | 4(2) | 7(2) | 4(2) | 9(3) | 7(3) | 72(82)[4] | 5(2) | 162(8) | |
| **Tumour stage – TNM**[5] n(%) I/II | 53(25) | 104(41) | 81(41) | 75(38) | 100(35) | 102(51) | 171(59) | 70(33) | 8(9) | *171(82)* | 764(39) | <0.001*[2,5] <0.001**[2,5] |
| III/IV | 126(60) | 137(54) | 106(54) | 121(61) | 178(62) | 96(48) | 108(38) | 134(64) | 8(9) | 32(15) | 1014(52) | |
| Missing | 32(15) | 11(4) | 11(6) | 4(2) | 7(2) | 4(2) | 9(3) | 7(3) | 72(82) | 5(2) | 157(8) | |
| **Treatment Surgery** n(%) Yes | 57(27) | 107(42) | 84(42) | 65(33) | 81(28) | 113(56) | 168(58) | 65(31) | 36(41) | 199(96) | 975(45) | <0.001*[2,5] <0.001**[2,5] |
| No | 61(29) | 56(22) | 55(28) | 94(47) | 90(32) | 44(22) | 111(39) | 79(37) | 28(32) | 5(2) | 623(29) | |
| Missing | 93(44) | 89(35) | 59(30) | 41(21) | 114(40) | 45(22) | 9(3) | 67(32) | 24(27) | 4(2) | 545(25) | |
| **Treatment Chemo** n(%) Yes | 105(50) | 125(50) | 98(49) | 93(47) | 159(56) | 93(46) | 107(37) | 133(63) | 50(57) | 63(30) | 1026(48) | <0.001*[2,5] <0.001**[2,5] |
| No | 41(19) | 51(20) | 46(23) | 65(33) | 45(16) | 62(31) | 172(60) | 37(18) | 18(20) | 137(66) | 674(32) | |
| Missing | 65(31) | 76(30) | 54(27) | 42(21) | 81(28) | 47(23) | 9(3) | 41(19) | 20(23) | 8(4) | 443(21) | |
| **Treatment Radio** n(%) Yes | 82(39) | 68(27) | 76(38) | 72(36) | 114(40) | 81(40) | 98(34) | 70(33) | 41(47) | 29(14) | 731(34) | <0.001*[2,5] <0.001**[2,5] |
| No | 50(24) | 72(29) | 50(25) | 77(39) | 69(24) | 71(35) | 180(63) | 69(33) | 22(25) | 155(75) | 815(38) | |
| Missing | 79(37) | 112(44) | 72(36) | 51(26) | 102(36) | 50(25) | 10(3) | 72(34) | 25(28) | 24(12) | 597(28) | |
| **Treatment Other** n(%) Yes | 10(5) | 14(6) | 14(7) | 11(6) | 30(11) | 18(9) | 9(3) | 0(0) | 7(8) | 16(8) | 129(6) | <0.001*[2,5] <0.001**[2,5] |
| No | 48(23) | 63(25) | 45(23) | 69(35) | 255(89) | 3(1) | 261(91) | 0(0) | 2(2) | 138(66) | 884(41) | |
| Missing | 153(72) | 175(69) | 139(70) | 120(60) | 0(0) | 181(90) | 18(6) | 211(100) | 79(90) | 54(26) | 1130(53) | |

[1]Differences between jurisdictions were tested by the Kruskal-Wallis test, [2] Differences between jurisdictions were tested by the Pearson's Chi[2] test, [3]Comorbidity coded as none=no reported, medium=1-2 reported and high=3+ reported, [4] This included cases which could not be mapped as they were classified as per Cancer Registry of Norway into local (stage I), regional (stage II-III) and distant (stage IV) [5]Excluding Victoria, [6]Excluding Norway, *Missing category is excluded, **Missing category is included,
Abbreviations: IQR=inter-quartile range.

*Routes to diagnosis*

Results are detailed in Table 3. Over half (55%) were diagnosed following presentation to the PCP of whom 63% (range: 29% Norway - 82% Wales; data not shown) were urgently referred with a suspicion of cancer, based on the PCP questionnaire.

**Table 3.** Routes to diagnosis of lung cancer patients for each jurisdiction. All figures are n(%) unless otherwise stated.

| | Wales (N=211) | England (N=252) | Scotland (N=198) | N Ireland (N=200) | Denmark (N=285) | Manitoba (N=202) | Ontario (N=288) | Sweden (N=211) | Norway (N=88) | Victoria (N=208) | Total (N=2143) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Symptoms prompting visit to PCP | 109(52) | 150(60) | 128(65) | 131(66) | 170(60) | 101(50) | 91(32) | 65(31) | 35(40) | 106(51) | 1086(51) |
| Symptoms prompting emergency (A&E) department visit[1] | 11(5) | 18(7) | 12(6) | 22(11) | 21(7) | 25(12) | 39(14) | 18(9) | 3(3) | 6(3) | 175(8) |
| Symptoms prompting visit to PCP and emergency (A&E) department[1] | 10(5) | 4(2) | 7(4) | 18(9) | 8(3) | 15(7) | 12(4) | 8(4) | 5(6) | 3(1) | 90(4) |
| Incidental diagnosis in course of investigation/treatment for another problem[2] | 68(32) | 37(15) | 36(18) | 19(10) | 55(19) | 57(28) | 116(40) | 107(51) | 32(36) | 90(43) | 617(29) |
| Unknown routes to diagnosis[3] | 10(5) | 17(7) | 11(6) | 5(3) | 16(6) | 4(2) | 14(5) | 11(5) | 8(9) | 0(0) | 96(5) |
| Other[4] | 3(1) | 25(10) | 3(2) | 4(2) | 14(5) | 0(0) | 16(6) | 2(1) | 5(6) | 3(1) | 75(3) |
| Missing | 0(0) | 1(0.4) | 1(0.5) | 1(0.5) | 1(0.4) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 4(0.2) |

[1] Emergency (A&E) route was ascribed when the patient reported pathway to cancer diagnosis involving going or being taken to the emergency department or the PCP reported that the patient presented to emergency department with or without their involvement [2] this could be by PCP, another doctor or via hospital; [3]includes cases where PCP or patient reported routes to diagnosis as 'Other' or 'Missing' but also reported symptoms or duration of symptoms, or date of first symptom, or waiting time for PCP appointment; [4]includes cases where PCP or patient reported routes to diagnosis as 'Other' and hasn't reported any symptoms or duration of symptoms, or date of first symptom, or waiting time for PCP appointment.

*Symptoms prompting visit to physician*

The median number of patient-reported symptoms were 2 (IQR 1,3). Across jurisdictions, the most common patient-reported symptoms were persistent cough (39%), breathlessness (37%) and fatigue (27%) although there was significant variation in proportion of patients presenting with individual symptoms (Table 4).

The PCPs reported a median of 1 (IQR 1,2) symptom at first presentation, with the most common being persistent cough (39%). Across jurisdictions, the reporting of other symptoms by the PCP was significantly lower compared to patients, especially fatigue (4%) and weight loss (8%). Unlike patients, there was minimal variation in PCP reporting of symptoms, with significant differences limited to 'no symptoms', 'other symptoms not previously listed' and weight loss. Overall 64% of symptoms were labelled as 'cancer specific' by the study PCPs (Table 4).

**Table 4.** Symptoms experienced by patients and presenting symptoms noted by PCP for eligible patients. All figures are n(%)

| | Wales | England | Scotland | N Ireland | Denmark | Manitoba | Ontario | Sweden | Norway | Victoria | Overall | p[1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Symptoms (reported by patient)** | (N=211) | (N=252) | (N=198) | (N=200) | (N=285) | (N=202) | (N=288) | (N=211) | (N=88) | (N=208) | (N=2143) | |
| persistent cough | 113(54) | 123(49) | 97(49) | 83(42) | 97(34) | 71(35) | 125(43) | 84(40) | 10(11) | 39(19) | 842(39) | <0.001 |
| breathlessness | 109(52) | 126(50) | 82(41) | 73(37) | 99(35) | 63(31) | 119(41) | 77(36) | 12(14) | 24(12) | 784(37) | <0.001 |
| fatigue | 75(36) | 79(31) | 64(32) | 61(31) | 38(13) | 55(27) | 92(32) | 60(28) | 17(19) | 42(20) | 583(27) | <0.001 |
| weight loss | 38(18) | 39(15) | 44(22) | 37(19) | 41(14) | 29(14) | 36(13) | 34(16) | 9(10) | 20(10) | 327(15) | 0.147 |
| felt sick /vomiting /nausea/loss of appetite | 42(20) | 33(13) | 31(16) | 24(12) | 33(12) | 22(11) | 45(16) | 28(13) | 3(3) | 20(10) | 281(13) | 0.132 |
| coughing up blood-stained phlegm (sputum) | 35(17) | 32(13) | 24(12) | 31(16) | 21(7) | 16(8) | 27(9) | 25(12) | 5(6) | 23(11) | 239(11) | 0.014 |
| chest or shoulder pain | 23(11) | 9(4) | 18(9) | 24(12) | 10(4) | 28(14) | 43(15) | 25(12) | 4(5) | 22(11) | 206(10) | <0.001 |
| other symptoms not listed above | 51(24) | 80(32) | 59(30) | 54(27) | 63(22) | 40(20) | 30(10) | 75(36) | 26(30) | 42(20) | 520(24) | <0.001 |
| no symptoms | 29(14) | 24(10) | 32(16) | 21(11) | 63(22) | 50(25) | 67(23) | 36(17) | 33(38) | 75(36) | 430(20) | <0.001 |
| missing | 1(0.5) | 16(6) | 6(3) | 17(9) | 31(11) | 9(4) | 4(1) | 4(2) | 12(14) | 1(0.5) | 101(5) | <0.001 |
| **Presenting symptom (reported by PCP)** | (N=85) | (N=133) | (N=115) | (N=0) | (N=151) | (N=86) | (N=61) | (N=0) | (N=17) | (N=81) | (N=729) | |
| persistent cough | 33(39) | 57(43) | 45(39) | n/a | 67(44) | 24(28) | 18(30) | n/a | 7(41) | 33(41) | 284(39) | 0.093 |
| breathlessness | 17(20) | 27(20) | 20(17) | n/a | 27(18) | 11(13) | 11(18) | n/a | 4(24) | 13(16) | 130(18) | 0.803 |
| fatigue | 1(1) | 5(4) | 3(3) | n/a | 9(6) | 2(2) | 2(3) | n/a | 1(6) | 3(4) | 26(4) | 0.449 |
| weight loss | 5(6) | 9(7) | 15(13) | n/a | 19(13) | 3(3) | 2(3) | n/a | 0(0) | 5(6) | 58(8) | 0.027 |
| felt sick /vomiting /nausea/loss of appetite | 1(1) | 1(0.8) | 2(2) | n/a | 6(4) | 2(2) | 0(0) | n/a | 0(0) | 0(0) | 12(2) | 0.312 |
| coughing up blood-stained phlegm (sputum) | 8(9) | 10(8) | 10(9) | n/a | 7(5) | 2(2) | 3(5) | n/a | 0(0) | 7(9) | 47(6) | 0.305 |
| chest or shoulder pain | 8(9) | 10(8) | 15(13) | n/a | 15(10) | 1(1) | 7(12) | n/a | 1(6) | 4(5) | 61(8) | 0.08 |
| other symptoms not listed above | 24(28) | 44(33) | 33(29) | n/a | 64(42) | 15(17) | 7(12) | n/a | 7(41) | 20(25) | 214(29) | <0.001 |
| no symptoms | 5(6) | 6(5) | 6(5) | n/a | 2(1) | 31(36) | 12(20) | n/a | 0(0) | 10(12) | 72(10) | <0.001 |
| missing | 7(8) | 7(5) | 11(10) | n/a | 16(11) | 12(14) | 6(10) | n/a | 2(12) | 10(12) | 71(10) | 0.392 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cancer-specificity of symptom presented** | | | | | | | | | | | | |
| cancer-specific symptom | 62(73) | 97(73) | 79(69) | n/a | 94(62) | 36(42) | 38(62) | n/a | 10(59) | 48(59) | 464(64) | <0.001 |
| non-specific symptom | 11(13) | 23(17) | 19(17) | n/a | 39(26) | 7(8) | 5(8) | n/a | 5(29) | 13(16) | 122(17) | |
| no symptoms /missing | 12(14) | 13(10) | 17(15) | n/a | 18(12) | 43(50) | 18(30) | n/a | 2(12) | 20(25) | 143(19) | |

[1] Differences between jurisdictions (excluding Victoria and Norway) were tested by the Pearson's $Chi^2$ test

*Time intervals*

The observed time intervals are shown in Supplementary File 5, Table 2 and are summarised in Figure 2. Based on overall trends, jurisdictions could be grouped into those with reduced, longer and similar intervals to Wales (Table 5). It was not possible to interpret variations observed in Norway (small sample size) and Victoria (surgical cohort). In the remaining jurisdictions, there was no difference in the median adjusted patient interval compared to Wales. Denmark had shorter median adjusted primary care interval (-11 days); Sweden had shorter (-20) and Manitoba longer (+40) diagnostic intervals compared to Wales. Denmark (-13), Manitoba (-11), England (-9) and Northern Ireland (-4) had shorter treatment intervals. The median adjusted total interval was shorter only in Denmark (Table 5, Figure 2). The differences were greater for the 90$^{th}$ percentile. The total interval in patients who waited longest (90$^{th}$ percentile) was significantly shorter in two jurisdictions (Denmark -142, England -28 days) compared to Wales.

**Table 5.** Differences in adjusted intervals (days) between Wales and the other nine jurisdictions for lung cancer patients

| Intervals | percentiles | Wales | Denmark | Sweden | England | N Ireland | Scotland | Manitoba | Ontario | Norway | Victoria |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Reference in days | Overall trend - shorter intervals | | | Similar with some intervals longer, some shorter | | Overal trend - longer intervals | | Difficult to interpret (see text for reasons) | |
| Ranking by 5-year survival rates for lung cancers diagnosed in 1999-2007 [5] | | 10 | 6 | 1 | 9 | 7 | 8 | 3 | 2 | 5 | 4 |
| Patient Interval | Number of patients | 181 | 233 | 172 | 213 | 179 | 169 | 133 | 205 | 55 | 141 |
| | 50th percentile (95% CI) | 21 | -6 (-13,0) | -1 (-9,8) | -3 (-10,5) | -3 (-13,6) | -3 (-10,4) | 1 (-8,10) | 1 (-11,14) | 0 (-8,8) | **-9** (-16,-2) |
| | 75th percentile (95% CI) | 61 | -13 (-38,13) | -2 (-24,21) | -2 (-42,37 ) | -8 (-55,39) | 1 (-25,27) | 3 (-23,30) | -7 (-54,39) | -9 (-60,42) | -4 (-46,38) |
| | 90th percentile (95% CI) | 216 | **-34** (-55,-13) | -1 (-25,23) | -15 (-42,12) | 24 (-21,70) | **43** (7,79) | **-35** (-59,-10) | **-34** (-66,-2) | **59** (21,96) | **-35** (-49,-21) |
| Primary Care interval | Number of patients | 110 | 159 | N/A | 147 | 124 | 119 | 80 | 75 | 19 | 89 |
| | 50th percentile (95% CI) | 20 | **-11** (-18,-3) | | -7 (-17,3) | -5 (-15,4) | -3 (-14,8) | 7 (-8,21) | 5 (-9,19) | **-11** (-18,-4) | -8 (-17,1) |
| | 75th percentile (95% CI) | 43 | **-29** (-47,-12) | N/A | -17 (-42,8) | 1 (-45,48) | -11 (-36,14) | 19 (-47,85) | 20 (-72,112) | -10 (-57,37) | -12 (-70,46) |
| | 90th percentile (95% CI) | 91 | -30 (-66,7) | | -39 (-85,6) | 17 (-55,90) | -20 (-67,25) | 13 (-38,65) | 102 (-56,258) | -22 (-109,66) | -19 (-89,51) |
| Diagnostic interval | Number of patients | 176 | 229 | 165 | 212 | 170 | 173 | 138 | 212 | 52 | 160 |
| | 50th percentile (95% CI) | 45 | -12 (-25,1) | **-20** (-35,-5) | 9 (-3,21) | 17 (-5,39) | -4 (-16,8) | **40** (14,66) | 10 (-6,26) | 4 (-16,24) | 7 (-13,27) |
| | 75th percentile (95% CI) | 108 | **-45** (-52,-39) | **-22** (-30,-15) | -7 (-20,7) | **12** (2,22) | -15 (-32,1) | **35** (22,48) | 5 (-9,19) | -4 (-15,8) | -2 (-8,4) |
| | 90th percentile (95% CI) | 162 | -27 (-153,99) | -34 (-206,138) | -14 (-100,72) | 112 (-165,389) | 31 (-81,143) | **112** (32,192) | 106 (-122,335) | 0 (-93,93) | **62** (10,114) |
| Treatment interval | Number of patients | 192 | 279 | 190 | 238 | 200 | 187 | 182 | 263 | 87 | 199 |
| | 50th percentile (95% CI) | 43 | **-13** (-15,-11) | -2 (-8,3) | **-9** (-12,-5) | **-4** (-7,-2) | 0 (-4,4) | **-11** (-17,-5) | 3 (-4,10) | **-8** (-11,-6) | **-29** (-32,-27) |
| | 75th percentile (95% CI) | 64 | **-32** (-36,-28) | -2 (-8,4) | **-18** (-23,-13) | **-13** (-18,-7) | 1 (-7,9) | -5 (-16,6) | 6 (-2,14) | **-13** (-19,-8) | **-33** (-41,-25) |
| | 90th percentile (95% CI) | 89 | **-45** (-50,-40) | **-10** (-17,-4) | **-28** (-36,-20) | **-16** (-23,-9) | -6 (-14,1) | 4 (-5,13) | 4 (-4,13) | **-22** (-30,-14) | **-39** (-45,-32) |
| Total interval | Number of patients | 147 | 192 | 147 | 176 | 153 | 143 | 117 | 178 | 52 | 113 |
| | 50th percentile (95% CI) | 116 | **-49** (-95,-3) | -8 (-64,47) | -7 (-52,38) | -16 (-41,10) | -2 (-70,66) | 11 (-41,63) | 9 (-78,97) | **-34** (-56,-12) | -32 (-64,2) |
| | 75th percentile (95% CI) | 204 | -91 (-270,87) | -17 (-40,7) | -29 (-175,118) | 5 (-191,201) | 33 (-144,211) | 13 (-77,103) | -7 (-331,317) | -39 (-107,29) | -23 (-61,14) |
| | 90th percentile (95% CI) | 365 | **-142** (-150,-134) | -18 (-59,23) | **-28** (-37,-18) | 0 (-4,5) | 15 (-26,55) | 15 (-26,55) | 0 (-78,79) | **-84** (-119,-49) | 0 (-3,3) |

| Interval relative to Wales | Trends | Significant |
|---|---|---|
| Reduction | | |
| Increase | | |

The majority of patients were diagnosed between 2013-14. The differences were calculated for the 50th, 75th and 90th percentiles by setting age to its mean value and gender and comorbidity to their modes (i.e. male gender and medium comorbidity). It is not possible to interpret differences observed for Norway (due to the small sample size) and Victoria (the cohort was limited to those who had undergone surgery).

FIGURE 2

*Sensitivity and validity analyses*

The estimates of routes to diagnosis, time intervals, and regression analysis trends were not significantly altered by changing the cut-off to 6 months or using only patient data (results not shown).Comparing the dates between the different data sources showed adequate agreement between all data sources for all categories of dates (CCC = 0.94 for date of treatment, CCC $\geq$ 0.93 for date of diagnosis, CCC = 0.91 for date of first presentation to primary care).

## Discussion

*Main findings*

This is the first international study we are aware of comparing lung cancer routes and time intervals. With the exception of Denmark, in all other jurisdictions, the median total interval from symptom onset to treatment, for respondents diagnosed in 2012-15 was similar to that of Wales, the reference. However, there were jurisdiction specific differences in patient, diagnostic and treatment intervals, especially for the 10% of patients who waited the longest. Based on overall trends, jurisdictions could be grouped into those with trends of reduced, longer and similar intervals to Wales. Across jurisdictions, all symptoms other than persistent cough were less frequently reported by the PCP when compared to patients. This was especially true for fatigue and weight loss. One in four patients reported incidental diagnosis and one in ten were diagnosed following a visit to the emergency (A&E) department.

*Strengths and weaknesses*

Strengths of this study include 1) its international setting; 2) use of cancer registries to identify consecutive newly diagnosed patients; 3) use of standardised questionnaires; 4) inclusion of PCP and CTS questionnaires enriched by registry data; 5) minimal data interpretation by the local teams with all data cleaning performed in a standardised manner centrally; and 6) triangulation with comprehensive data rules to ensure validity, consistency and preserve statistical precision.[20] Recall bias was minimised by the triangulation of different data sources and by patients completing the questionnaire within a limited time window (median 5 months) after the cancer diagnosis.

A key limitation, as with all questionnaire-based studies was non-response bias which varied across jurisdictions. In comparing intervals, we adjusted for age, sex and comorbidity but were unable to adjust for ethnicity and education due to different classification systems. Recruitment of patients up to 9 rather than 6 months after diagnosis might have magnified the selection bias due to high mortality.[28] However, sensitivity analysis suggests that this did not impact on the results. Categorising presenting symptoms into indicative or not was done pragmatically as existing guidelines for lung cancer investigation vary across ICBP jurisdictions.[29] In Norway and Victoria, a small sample size and restriction of eligibility to only surgical patients, respectively, made comparison difficult. Nonetheless, significant differences in these two jurisdictions compared to Wales were largely limited to the treatment interval alone, suggesting that despite sampling issues, the pathway to diagnosis was comparable.

There was variation in stage distribution across jurisdictions. While this may be partly related to the varying response rate, true differences in lung cancer stage have been noted on analysis of registry data of patients diagnosed between 2004-2007.[5] The high lung cancer mortality and self-selection are likely to have contributed to an over-representation of early stage disease and tumours treated with surgical resection. This suggests that true variation may well be higher than that reported in this cohort of 'healthier early stage' patients.

*Comparison to other studies*

The most common patient-reported symptoms, in keeping with the literature, were persistent cough, breathlessness, fatigue and weight loss, with one in five reporting 'no symptoms'.[13] Only a minority (11%) of our respondents reported coughing blood or bloody sputum/spit, which is the only consistent predictor of lung cancer.[30] While haemoptysis was reported in a prospective survey (England 2011-12) by 22% of lung cancer patients identified through respiratory clinics, it was a presenting symptom in only 5% of cases.[6]

As lung cancer mortality is higher in patients attending emergency (A&E) departments, the rates are often compared in an attempt to understand international survival differences.[31] The rate of respondents who attended A&E varied two-fold across jurisdictions from 9-10% in England, Scotland and Denmark to 18-20% in Northern Ireland, Ontario and Manitoba. While rates for Scotland (10%) were similar to that reported in a prospective Scottish audit (11.5%), as were rates for Denmark (7% vs 6.3% when PCP not involved), rates for England (9%) were lower than those reported in population based audits (25%) reflecting non-response bias.[9,10] In Victoria (4%) restriction of the cohort to surgical patients is likely to have accounted for the very low rates.

Our reported median patient, primary care and diagnostic intervals are in keeping with those previously reported from the participating jurisdictions (Table 6). Minor variations in interval estimates are likely due to differences in data source, sample size and cohort characteristics.[32] Longer intervals were reported from earlier cancer cohorts - median primary care interval for England of 52 days in 1998-2000 (our median 11),[8] median total interval for Denmark of 108 days in 2004-5 (our median 67) and Norway of 118 in 2002-5 (our median 79).[12-14]

**Table 6.** Summary of literature on intervals in lung cancer patients diagnosed since 2000 in the ICBP Module 4 countries

| Study No | Ref | Study Period | Jurisdiction | Design | Patients | No. of lung cancer patients | Interval[1] (days) | | | | Total interval |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Patient | Primary care | Diagnostic | Treatment | |
| 1 | Walter FM et al (2015) | 2011-2 | England, UK | Prospective patient questionnaire survey - multi hospital cohort. Dates of diagnosis based on medical note review. | All attending urgent and routine respiratory clinics across the five hospitals in England aged over 40 years with symptoms suspicious of lung cancer. | 153 | Interval from first symptom to diagnosis Median 91 (IQR 49-184) | | | | |
| 2 | Lyratzopoulos G et al (2015) | 2009-10 | England, UK | Prospective national audit of cancer diagnosis using primary practice patient records and continuous sampling during audit period | All patients aged ≥15 years who had first presented to a primary care practitioner and were subsequently diagnosed with one of 28 cancers | 1128 | Median 11 (IQR 0-32) | Median 3 (IQR 14-39) | | | |
| 3 | Neal R et al (2014) | 2007–8 | UK | Retrospective analysis of electonic health record data from General Practice Research Database - population cohort | All newly diagnosed with one of 15 cancers | 2851 | | | Median 112 (IQR 45-251) | | |
| 4 | Barrett J et al (2008) | 1998-2002 | Exeter, England, UK | Retrospective case-control review of PCP records - population cohort | All with lung cancer aged ≥ 40 years, identified from the hospital cancer registry and computerised searches of all primary care practices | 247 | | Median 52 (IQR 7–243) | | | |
| | | | | | | | Interval from first symptom to diagnosis - Median 121 (IQR 53,261) | | | | |
| 5 | Baughan P et al (2009) | 2005-6, 2007-8 | Scotland, UK | Retrospective audit involving PCP review of medical records of all newly diagnosed cancer patients they had seen - population cohort | All newly diagnosed with lung cancer | 981 | Median 9.5 (IQR 31) | | Median 11 (IQR 28) | | |
| 6 | Guldbrandt LM et al (2015) | 2010 | Denmark | Retrospective PCP questionnaires survery of national registry-based population cohort | All consecutive newly diagnosed lung cancer patients | 429-442 depending on interval | | Median 7 (IQR, 0-30) | Median 29 (IQR, 12-69) | | |
| 7 | Tørring ML et al (2013) | 2004 - 5 | Aarhus, Denmark | Prospective, population-based study using electronic health records and PCP survey of identified patients | All newly diagnosed with lung cancer after attending primary care | 262 | | | Median 112 (IQR 45-251) | | |
| 8 | Hansen RP et al (2011) | 2004-5 | Aarhus, Denmark | Retrospective PCP survey | Cancer patients newly diagnosed during a 1-year period identified using administrative registry data | 128-251 (depending on interval) | Median 28 (IQR 7-56) | Median 0 (IQR 0-9) | | Median 51 (IQR 27-76) | Median 108 (IQR 82-167) |
| 9 | Bjerager M et al (2006) | 2003 | Aarhus, Denmark | Retrospective PCP survey using structured telephone interviews enriched with administrative registry data - population-based cohort | All lung cancer patients identified through histological and cytological tests from county-based registers | 84 | | Median 32.5 (IQR 12–68) | | | |
| 10 | Rolke HB et al (2006) | 2002-5 | Norway (South) | Retrospective questionnaire-based patient survey - hospital cohort | All newly diagnosed with lung cancer | 273 -376 (depending on interval) | Median 19 (2–77) | | | | Median 118 (IQR 68–220) |
| 11 | Stokstad T et al (2017) | 2011-13 | Norway | Retrospective medical record audit - single hospital cohort | All cases that started diagnostic work-up and were diagnosed with lung cancer at St. Olavs Hospital, Trondheim | 449 | | | | 42 days (range: 2–296) | |
| 12 | Largey G et al (2016) | 2013 | Victoria, Australia | Retrospective medical record audit - three hospital cohort | Admitted with a new diagnosis of lung cancer over a three month period in three hospitals | 78 | | | | Mean 30.4 (SD 45.3) | |
| 13 | Evans SM et al (2016) | 2011-4 | Victoria, Australia | Retrospective medical record audit - multi hospital cohort | All lung cancer patients newly diagnosed in six public and two private hospitals | 1417 | | | Median 15 (IQR, 5–36) | Median 30 (IQR, 6–84) | |
| 14 | Emery JD et | 2012 - | Western | Prospective cluster randomised trial of | Lung cancer patients newly diagnosed in | 167 | Interval from first symptom to | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | al (2017) | 4 | rural Australia | symptom awareness | the control arm of the trial | | diagnosis Median 34.5 (IQR 7 103.5) | | | | |
| 15 | Burneister BH et al (2010) | 2000-4 | Queensland Australia | Retrospective analysis of radiation therapy waiting times | All lung cancer patients who received radiation therapy as initial treatment at a public hospital. | 1535 | | | | | Median 33[2] |
| 16 | Ellis PM and Vandermeer R (2011) | 2010 | Ontario, Canada | Retrospective patient survey using structured telephone interviews - single centre cohort. Appointment dates and diagnostic tests verified through family doctor or patient chart review. | All lung cancer patients referred to a regional cancer centre | 52 | | Median 21 | Median 27 (IQR 0-38) | | Median 138 (IQR 79-175) |
| 17 | Lo DS et al (2007) | 2005-7 | Ontario, Canada | Retrospective medical record audit - multi hospital cohort | All with lung cancer seen on a newly implemented Time to Treat Program | 144 | | | Median interval from suspicion of lung cancer to diagnosis 37 | | |

[1] Intervals as defined in Figure 1; [2] Limited to patients receiving radiation treatment

Across all jurisdictions, there was no significant difference in primary care intervals for the 10% of patients with longest interval. It is likely that these patients had vague or non-specific symptoms and signs. Referral guidelines for suspected lung cancer do not always favour patients with early symptoms and often prioritise those with more advanced disease.[33] Access to better diagnostic tools such as low-dose CT chest in the primary care setting may favour this group of patients.[34] It would be useful in future projects to explore whether such access may have contributed to the improved 1-year lung cancer survival rates reported from Australia and Canada.[5]

Diagnostic intervals were significantly longer for Manitoba. Of note, in 51% of the PCP responses presenting symptoms were missing or recorded as not present and date of first presentation was derived from patient as opposed to PCP. While this may explain why the diagnostic interval was twice that reported from ongoing local audit (personal communication), for date of first presentation, the concordance co-efficient between PCP and patients at Manitoba was 0.94, which suggest adequate agreement.

Observed median treatment intervals were below 6 weeks for nearly all jurisdictions. This was the only interval where there were significant differences between jurisdictions with Denmark, England, Norway and Northern Ireland all having shorter adjusted treatment intervals across all percentiles, with larger differences for the 75$^{th}$ and 90$^{th}$ percentile. These improvements may reflect implementation of waiting time targets in Denmark (35-38 days from first consultation depending on treatment modality) and the UK (31 days from decision to treat).[35,36] The shorter treatment intervals in Norway are in keeping with long-standing provision of standardised cancer care pathways and effective coordination between primary care and treatment centers. While a systematic review did not find evidence to support an association between intervals and lung cancer outcomes, increasing mortality with longer diagnostic intervals was noted in a more recent, high-quality study.[11] In 2000, O'Rourke reported median delays of 94 days (35-187) between the first hospital visit and starting treatment resulting in 21% of potentially curable patients becoming incurable.[37] Others have found metabolic evidence on PET/CT of pre-treatment disease progression in 21% and TNM upstaging in 18% of small-cell lung cancer patients after a relatively short median inter-scan interval of 43 days.[38] Delays can also result in deterioration in performance status. More recently, there is concern that the use of genotyping prior to starting treatment may introduce additional delays.

The shorter total interval in Denmark likely reflects the significant reductions in cancer waiting times following implementation of national Danish Cancer Patient Pathways (CPPs) including PCP access to fast-track diagnostic work-up.[39] The findings are in keeping with higher relative survival and lower mortality in Denmark among symptomatic cancer patients diagnosed through primary care after the implementation of CPPs and with the accelerated increase in 5-year survival among Danish lung cancer patients diagnosed in 2010-2014 when compared to patients from earlier time periods.[40] While there is some inherent lead-time bias, the findings highlight the importance and feasibility of a timely diagnosis of lung cancer.

*Conclusions*

The study provides for the first time, comparable data allowing for detailed evaluation between jurisdictions of routes and intervals from symptom onset to treatment in lung cancer. Across countries there were discrepancies in symptoms, especially fatigue and weight loss reported by patients and their primary care physicians. The findings highlight differences especially for patients who waited the longest and quantifies achievements, thus allowing for more focused policy and practice initiatives. Some jurisdictions may be able to revise the organisation of pathways to shortern time intervals and ultimately improve patient experience and outcomes.

Future analysis will explore the impact of these intervals on stage and survival. Meanwhile, our results draw attention to the success of secondary care initiatives in decreasing treatment intervals and underlines the need for more concerted efforts in primary care.

**List of abbreviations**

ICBP M4 – International Cancer Benchmarking Partnership Module 4

PCP – Primary Care Physician

CTS – Cancer Treatment Specialist

CPP – Danish Cancer Patient Pathways

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**Author's contribution**

UM, DW, PV, AZF, HJ planned the study design, data collection, carried out the analyses and wrote the draft manuscript. UM, PV, DW, HJ, AB, AKK, RJB, DHB, JK, VC, ATG, EG, EH, ML, RJW, YL, MM, DT, RDN, VW, IR and SH were responsible for local data collection (alongside the Working Group), management and interpretation, and have participated in writing and have approving the final manuscript version. JB, OB and OTB provided advice on the interpretation of results in their respective jurisdictions and comments or substantial edits on the manuscript, approving the final version.

**Competing Interests**

None

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**Availability of data and material**

The data that support the findings of this study are available from the named authors from each ICBP jurisdiction, but restrictions apply to the availability of these data and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the ICBP Programme Board. Please contact the ICBP Programme Management team, based at Cancer Research UK, with any queries (icbp@cancer.org.uk).

**Ethics approval and consent to participate**

For each local data collection, there were specific procedures and approvals which included anonymised data transfer to University College London and Aarhus University. Approvals were received from the following institutions: Cancer Council Victoria Human Research Ethics Committee [HREC 1125]; Health Research Ethics Board, University of Manitoba [HS15227 (H2012:105)]; Research Resource Ethics Committee, CancerCare Manitoba [RRIC#28-2012]; University of Toronto Research Ethics Board [27881]; The Danish Data Protection Agency [2013-41-2030]; Swedish Ethics Review Board, Uppsala [2013/306]; Norway Regional committees for medical and health research ethics [2013/136/REK nord]; England, Wales and Scotland, NRES Committee East Midlands – Derby 2, local R&D for each health board [11/EM/0420]; Northern Ireland ORECNI Ethical approval, local governance for each health Trust [11/EM/0420].

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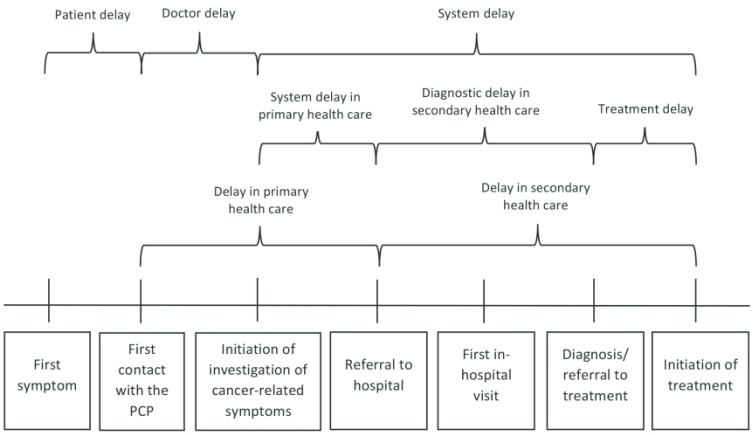
**Figure 1:** Time intervals from onset of symptoms to start of treatment based on the Aarhus Statement [21]

**Figure 2**: Differences in 50th, 75th and 90th percentiles of the intervals (days) between Wales as the reference and the other nine jurisdictions.

*The data are adjusted for differences in age, gender and comorbidity. The bars in black show significant differences in intervals.*




Time intervals from onset of symptoms to start of treatment based on the Aarhus Statement [21]

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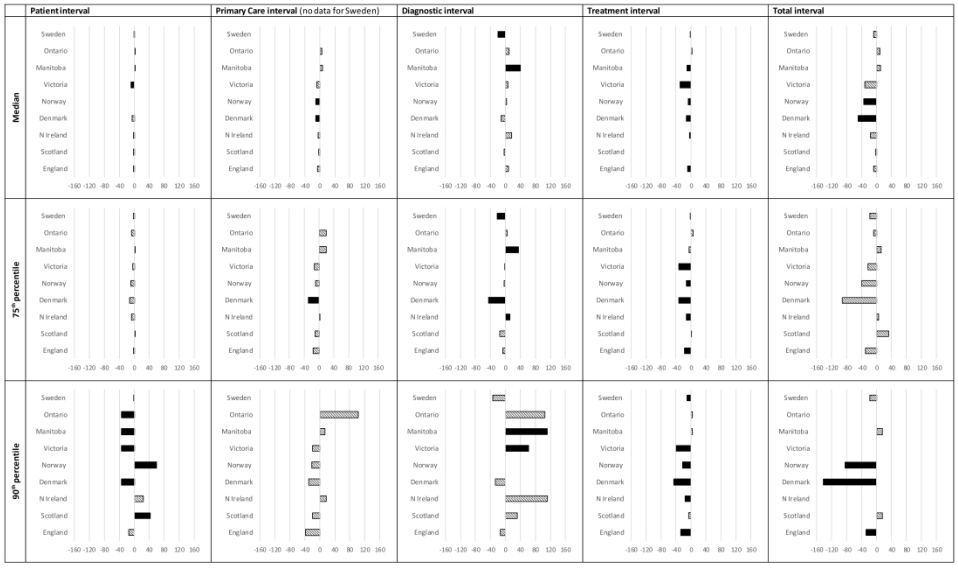


Differences in 50th, 75th and 90th percentiles of the intervals (days) between Wales as the reference and the other nine jurisdictions.

420x297mm (300 x 300 DPI)

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**Supplementary File 1: Patient Questionnaire**

# International Cancer Benchmarking Partnership Module 4

## Patient questionnaire

## Lung Cancer

Thank you very much for taking the time to fill in this questionnaire – it should take about 20 minutes to complete. We are sending the questionnaire to a large sample of people who we understand have had a diagnosis of lung cancer. If this has been sent to you in error and you do not have cancer, please do not continue and return the documents in the prepaid envelope.

Our aim is to gain a better understanding of the process by which people have their cancer diagnosed. We would also like to find out more about the symptoms they experience (if any), and the pathway they follow from start of symptoms to treatment of their cancer. This will help in identifying ways in which cancers can be diagnosed quickly and effectively. Thank you once again for your time.

**This information is confidential and will not be passed to anyone involved in your treatment.**

Name: _____

Date of Birth: _____

Address: _____

_____

_____

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# Consent form

Please read the consent form and sign your name and date **BELOW**.

If you require any clarification, please do not hesitate to ring the study team members. Their contact details are found on the information sheet.

**Please be reassured that your responses are completely confidential and will not be passed to anyone involved in your treatment. For the purposes of the study it is important that you agree to consent to all the statements listed below.**

- I confirm that I have read the attached information sheet and I understand why the research is being done.
- I am willing for the team to request information from my GP and hospital doctors which is relevant to the audit as described in the information sheet.
- I give permission for my details (name, address) to be given to the cancer registry (NHS Information Centre for Health and Social Care) for follow up.
- I agree for the information I have provided and any other relevant information from my medical records to be stored as described in the information sheet under the custodianship of University College London.
- I consent to sharing of coded data which contains no personal identifiers between researchers, some of whom are located outside the European Union.
- I consent for use of my data if I become mentally incapacitated during the course of the project.

**I agree to all the statements listed and consent to participate in the study.**

Name (Please print) _____

Signature: _____ Date: _____

If we have any questions, may we phone you for clarification?
(Please tick) ☐ **Yes** ☐ **No**

If **Yes**, please provide your telephone number: _____

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**1. Please can you confirm the details of your GP/GP practice (name, practice address – as best as you can remember): We appreciate that you may have more than one GP involved in your care – in which case, we are interested in the GP you would say provides the majority of your care, particularly relating to the cancer you've had diagnosed.**

Name of doctor

Name of practice

Address

Postcode

Town

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**2. Which of the following best describes the events which led to your diagnosis of cancer?** (please tick only **ONE** answer)

| | ✓ |
|---|---|
| I had symptoms/I noticed a bodily change and went to see a doctor (e.g. GP) | |
| I had symptoms/I noticed a bodily change and went/was taken to Accident and Emergency (A&E) | |
| I had seen a doctor/GP with symptoms, but went/was taken to Accident and Emergency (A&E) when things worsened | |
| I was being investigated by my doctor(s) for another problem during which time the cancer was discovered | |
| Other (please describe): | |

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**3. The following health concerns or symptoms are commonly experienced with lung cancer.**

| |
|---|
| Cough |
| Breathlessness |
| Being short of breath |
| Chest pain / Pain on breathing |
| Coughing up blood |
| Bloody sputum/blood in spit |
| Unexplained weight loss |
| Loss of appetite |
| Fatigue |

**Please write down ALL health concern(s) or symptom(s) you may have had before contacting a doctor or taking part in screening. It does not matter if they are not included in the list above:**

| Please write your health concern(s) or symptom(s) in the boxes below: |
|---|
| 1) |
| 2) |
| 3) |
| 4) |
| 5) |
| 6) |

| | |
|---|---|
| This is not applicable to me (e.g. I did not have any symptoms), please tick | ✓ |

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**4. Please write down your best estimate of the date you noticed the first of these health concern(s) or symptom(s).** If you cannot remember the exact date, you can fill in the month and the year.

Day (optional), month, year

| D | D | M | M | Y | Y | Y | Y |
|---|---|---|---|---|---|---|---|

| | |
|---|---|
| This is not applicable to me (e.g. I had no symptoms), please tick | |

**5. Approximately how long did you have health concern(s) or symptom(s) before contacting a doctor? (Please think of the first visit to the doctor, not re-visits after that).** Please tick only **ONE** answer.

| | |
|---|---|
| Less than 1 week | |
| 1-2 weeks | |
| 3-4 weeks | |
| 5-7 weeks | |
| 2-5 months | |
| 6-12 months | |
| More than 12 months | |

| | |
|---|---|
| This is not applicable to me (e.g. I had no symptoms), please tick | |

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**6a. Once you contacted a practice about your health concern(s) or symptom(s), how long did it take to get an appointment with a doctor? (Please think of the first visit to the doctor, to discuss your health concern(s) or symptom(s)).**
Please tick only **ONE** answer.

| | |
|---|---|
| Same day/next day | |
| Within 1 week | |
| 1-2 weeks | |
| 3-4 weeks | |
| Longer | |

| | |
|---|---|
| If there was no waiting time (e.g. you went/were taken to A&E), please tick this box | |

| | |
|---|---|
| This is not applicable to me (e.g. I had no symptoms), please tick | |

**6b. What was the date you first saw your doctor about your health concern(s) or symptom(s)?** If you cannot remember the exact date, you can fill in the month and the year.

Day (optional), month, year

| D | D | M | M | Y | Y | Y | Y |
|---|---|---|---|---|---|---|---|

| | |
|---|---|
| This is not applicable to me (e.g. I had no symptoms), please tick | |

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## 7. How many times did you visit the following for the investigation of your symptoms before your cancer was diagnosed?

| | Please write down the number of visits |
|---|---|
| GP | |
| Hospital | |
| Consultant/specialist outside of a hospital | |

| | ✓ |
|---|---|
| This is not applicable to me (e.g. I had no symptoms), please tick | |

## 8a. After your doctor referred you to a specialist, how long did it take you to get an appointment? Please tick only **ONE** answer.

| | ✓ |
|---|---|
| Less than 1 week | |
| 1-2 weeks | |
| 3-4 weeks | |
| 5-7 weeks | |
| 2-5 months | |
| 6-12 months | |
| More than 12 months | |

| | ✓ |
|---|---|
| This is not applicable to me (e.g. my doctor did not refer me), please tick | |

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**8b. What was the date of your first appointment with a doctor, involved in investigating and/or treating your cancer, to whom you were referred?**
If you cannot remember the exact date, you can fill in the month and the year.

Day (optional), month, year

| D | D | M | M | Y | Y | Y | Y |
|---|---|---|---|---|---|---|---|

| This is not applicable to me (e.g. my doctor did not refer me), please tick | ✓ |
|---|---|

**9. What was the date you were told you had cancer?** If you cannot remember the exact date, you can fill in the month and the year.

Day (optional), month, year

| D | D | M | M | Y | Y | Y | Y |
|---|---|---|---|---|---|---|---|

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**10. Have you had any of the following treatments for your cancer yet? If so, please can you estimate the date this treatment started?** Please tick **ALL** that apply. If you cannot remember the exact date, you can fill in the month and the year.

| | Type of treatment | | Date of treatment (give first date if you had more than one) |
|---|---|---|---|
| a. | Surgery | ☐ Yes ☐ No | Day (optional), month, year D D M M Y Y Y Y |
| b. | Chemotherapy | ☐ Yes ☐ No | Day (optional), month, year D D M M Y Y Y Y |
| c. | Radiotherapy | ☐ Yes ☐ No | Day (optional), month, year D D M M Y Y Y Y |
| d. | Other Please specify: | ☐ Yes ☐ No | Day (optional), month, year D D M M Y Y Y Y |
| e. | Treatment not started yet | ☐ Yes | |

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**11. Who is the consultant doctor who has taken responsibility for diagnosing and or/treating your cancer?**

| |
|---|
| Name of consultant: |
| Hospital name: |
| Hospital department: |

**Please can you answer some more general questions about your health?**
It will help us in interpreting your responses to this questionnaire to know about your general health and other health problems you may have had in the past.

**12. Looking back to the 2 years before you were diagnosed with cancer, would you say your general health was** (Please tick only **ONE** answer.)**:**

| | ✓ |
|---|---|
| Very good | |
| Good | |
| Fair | |
| Poor | |
| Very poor | |

**13. Have you been treated before for any of the conditions below?**
Please tick 'yes' or 'no' for each condition:

| | | |
|---|---|---|
| Heart disease | ☐ **Yes** | ☐ **No** |
| Stroke | ☐ **Yes** | ☐ **No** |
| Lung disease (excluding lung cancer) | ☐ **Yes** | ☐ **No** |
| Diabetes | ☐ **Yes** | ☐ **No** |

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**Finally, a little more information about you.** The information you provide below will help us to analyse the results of the survey in more detail.

**14. Which of these best describes your ethnic group? (please tick one box, as appropriate).** If you are descended from more than one ethnic or racial group, please tick the group you consider you belong to, or tick 'any other ethnic group'.

| | ✓ | | ✓ | | ✓ | | ✓ |
|---|---|---|---|---|---|---|---|
| White | | Chinese | | Black - Caribbean | | Black - African | |
| Black - other | | Indian | | Pakistani | | Bangladeshi | |
| Any other ethnic group, please specify: | | | | | | | |

**15. What is the main language spoken in your home?** Please tick

| | ✓ |
|---|---|
| English | |
| Other, please specify: | |

**16. What is the highest level of education you have achieved?**
Please tick only **ONE** answer.

| | ✓ |
|---|---|
| Finished school at or before the age of fifteen | |
| Completed GCSEs, O-levels or equivalent | |
| Completed A Levels or equivalent | |
| Completed further education but not a degree | |
| Completed a Bachelor's degree / Masters degree / PhD | |
| Other, please specify: | |

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**17. Have you ever smoked cigarettes, including hand-rolled ones, pipes or cigars?**

☐ Yes ☐ No

**18. Are you a current smoker, smoking either cigarettes, including hand-rolled ones, pipes or cigars?**

☐ Yes ☐ No

**19. If you are a current smoker or have smoked in the past, how many cigarettes, including hand-rolled ones, pipes or cigars on average do you smoke/have you smoked per day?**

| Number per day: | |
|---|---|

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## 20. Further comments

**Please add anything else that you would like to tell us about your cancer diagnosis or treatment.**



**Thank you very much for taking the time to complete this questionnaire.**

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**Supplementary File 2: Primary Care Questionnaire**

# International Cancer Benchmarking Partnership Module 4

## Primary Care Audit

## Lung Cancer

Thank you very much for agreeing to fill in this questionnaire. As part of an international study examining differences in cancer survival, we are sending the questionnaire to health care providers of a sample of consented patients with cancer.

Our aim is to gain a better understanding of the process by which people have their cancer diagnosed – the symptoms they experience, and the pathway they follow from onset of symptoms to treatment of their cancer. This will help in identifying ways in which cancers can be diagnosed and treated quickly and effectively. Thank you once again for your time.

**Please can you refer to your patient's notes in completing the questionnaire as this will help in obtaining accurate data on time points.**



If you would prefer to return this questionnaire without the patient details, please tear off along the dotted line

ID-number: Jurisdiction-ID + Patient-ID:

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## Patient information

ID-number: Jurisdiction-ID + Patient-ID:

Full name:

Address:

Postcode:

Date of birth: D D M M Y Y Y Y

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## 1. Duration of symptoms

Please estimate how long your patient had symptom(s), attributable to lung cancer, before attending your practice (or other health service).

We appreciate that identifying a 'date of first symptom' is not always straightforward – particularly when there are multiple and/or chronic symptoms. Nevertheless, we hope you can provide a 'best estimate'.

| **Estimate of symptom duration** (please tick **one**): | ✓ | **What were the symptoms?** Please describe: |
|---|---|---|
| Less than 1 week | | |
| 1 to 4 weeks | | |
| 5 to 7 weeks | | |
| 2-5 months | | |
| 6-12 months | | |
| More than 12 months | | |
| Not possible to estimate | | |
| No symptoms (e.g. screen detected cancers) | | |

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## 2. Pathway of presentation

### 2.1 Through what route did the patient first present? Please tick **ONE**:

| | ✓ | |
|---|---|---|
| Your patient first presented to primary care (either in-hours or out-of-hours) | | Please can you provide your best approximation of the date of this **primary care** visit<br>D D M M Y Y Y Y |
| Your patient presented straight to A&E (with or without your involvement) | | |
| Your patient first presented to primary care, but then at a later date presented to A&E as an emergency (with or without your involvement) | | Please can you provide your best approximation of the date of this **primary care** visit<br>D D M M Y Y Y Y |
| Other – please describe: | | |

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## 3. Date you ordered any tests/investigations in response to symptom(s).

We are interested in any kind of tests/investigations (e.g. imaging etc) that you may have ordered. Please only consider the tests/investigations that you ordered yourself. Please tick **all** that apply and put in the date that the test/investigation was ordered:

| | ✓ | |
|---|---|---|
| Chest x-ray | | D D M M Y Y Y Y |
| MRI scan | | D D M M Y Y Y Y |
| CT scan | | D D M M Y Y Y Y |
| PET scan | | D D M M Y Y Y Y |
| Sputum test | | D D M M Y Y Y Y |
| Lung biopsy | | D D M M Y Y Y Y |
| Bronchoscopy | | D D M M Y Y Y Y |
| Other (please specify): | | D D M M Y Y Y Y |

## 4. Date of referral to specialist medical services

At what date did you **first** refer the patient to hospital or another specialist transferring the responsibility for on-going investigation/treatment to other medical services?

D D M M Y Y Y Y

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## 5. Nature of this referral

### 5.1 Do you know the date that the patient was seen for this referral?

☐ **Yes**, please provide the date: | D | D | M | M | Y | Y | Y | Y |

☐ **No**

### 5.2 If you did make a referral to specialist services, which of the following best describes the nature/characteristics of this referral? Please tick **one**.

| | ✓ |
|---|---|
| Emergency admission: a referral to A&E (or equivalent) for immediate admission | |
| An urgent referral for assessment of cancer symptoms/signs/test results (Note this will be within 2 weeks for England/Wales) | |
| A less urgent referral in which cancer is raised as a possibility (Note this will be greater than 2 weeks for England/Wales) | |
| A more general referral for investigation and assessment without cancer mentioned | |
| No referral was made | |
| Other – please describe | |

### 5.3 Would you say this patient's diagnostic pathway was conducted predominantly in the public or private system? Please tick **one**.

| | ✓ |
|---|---|
| Public healthcare system | |
| Private healthcare system | |

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## 6. Date of lung cancer diagnosis

This can be decided in different ways. Please tick **all** that apply.
Please provide whichever of the following dates you have to hand:

| | ✓ | |
|---|---|---|
| Date of histological confirmation [ideal] | | D D M M Y Y Y Y |
| Date results of investigation (histological or other) confirming cancer received | | D D M M Y Y Y Y |
| Date patient was told | | D D M M Y Y Y Y |
| Date biopsy undertaken | | D D M M Y Y Y Y |
| Date patient was first admitted to hospital because of the malignancy | | D D M M Y Y Y Y |
| Other (please specify) | | D D M M Y Y Y Y |

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## 7. Additional information

Finally, we are interested to know what other conditions your patient has, and the severity/impact of these conditions

Have you and/or any of your partners treated this patient (or has the patient been to hospital) for any of the following conditions? Please tick **all** that apply:

| | |
|---|---|
| Cardiovascular disease | ☐ **Yes** ☐ **No** |
| Stroke | ☐ **Yes** ☐ **No** |
| Lung disease (except lung cancer) | ☐ **Yes** ☐ **No** |
| Diabetes | ☐ **Yes** ☐ **No** |

**Are there any other comments you would like to make about this patient?**

Name (and title):

Signature:

Date:

**Thank you very much for taking the time to complete this questionnaire.**

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# International Cancer Benchmarking Partnership Module 4

## Specialist Care Audit

## Lung Cancer

Thank you very much for agreeing to fill in this questionnaire – it should take about 10 minutes to complete. As part of an international study examining differences in cancer survival, we are sending the questionnaire to health care providers of a sample of patients with cancer.

Our aim is to gain a better understanding of the process by which people have their cancer diagnosed – the symptoms they experience, and the pathway they follow from onset of symptoms to treatment of their cancer. We hope you can help us with information on this patient's cancer journey once they were referred to specialist cancer services. This will help in identifying ways in which cancers can be diagnosed and treated quickly and effectively.



**Thank you once again for your time**

**Please can you refer to your patient's notes in completing the questionnaire, as this will help in obtaining accurate data on time points.**

If you would prefer to return this questionnaire without the patient details, please tear off along the dotted line.

Your patient _____

is participating in the study.

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## Patient information

ID-number: Jurisdiction-ID + Patient-ID:

Full name:

Address:

Postcode:

Date of birth: D D M M Y Y Y Y

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1. **Date patient first attended hospital/specialist services related to their cancer diagnosis.** We appreciate this date can at times be difficult to identify, particularly when there have been multiple visits in the lead up to a definitive diagnosis. Put another way, it's the date that the hospital/specialist service assumed responsibility for on-going investigation/treatment for your patient.

Day (optional), month, year

| D | D | M | M | Y | Y | Y | Y |
|---|---|---|---|---|---|---|---|

2. **How was the patient referred to the hospital/specialist services related to their cancer diagnosis?** Please tick.

Was it through a:

| | ✓ | | ✓ |
|---|---|---|---|
| GP referral | | Referral from respiratory clinic | |
| Medical specialist/Consultant referral | | Other referral – please specify: | |



3. **Where did this first contact/appointment happen?** Please tick.
Which of the following best describes where this first contact/appointment took place?

| | ✓ | | ✓ |
|---|---|---|---|
| Emergency department ('A&E') | | Medical outpatient department, please specify which department | |
| Oncology general outpatient department | | Surgical outpatient department, please specify which department | |
| Other – please specify: | | | |

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## 4. Date of diagnosis

This can be decided in different ways.
Please tick and complete as many of the following dates as possible.

| | ✓ | |
|---|---|---|
| Date of histological confirmation (ideal) | | Day (optional), month, year D D M M Y Y Y Y |
| Date results of investigation confirming cancer received | | Day (optional), month, year D D M M Y Y Y Y |
| Date patient was told | | Day (optional), month, year D D M M Y Y Y Y |
| Date of biopsy | | Day (optional), month, year D D M M Y Y Y Y |
| Date patient was first admitted to hospital because of the malignancy | | Day (optional), month, year D D M M Y Y Y Y |
| Date of MDT confirmation of diagnosis | | Day (optional), month, year D D M M Y Y Y Y |
| Other (please specify): | | Day (optional), month, year D D M M Y Y Y Y |

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## 5. Date treatment for the cancer commenced

Based on your records, when would you say that any treatment specifically targeting the patient's cancer started?

Day (optional), month, year

| D | D | M | M | Y | Y | Y | Y |
|---|---|---|---|---|---|---|---|

## 6. Additional information

Please can you provide any further information on the patient's cancer:

| **TNM**, please tick as appropriate: | |
|---|---|
| 0 | |
| I | |
| IIA | |
| IIB | |
| IIC | |
| IIIA | |
| IIIB | |
| IIIC | |
| IV | |
| Not able to stage | |

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## 6.1 Histological subtype:

| | ✓ |
|---|---|
| Squamous cell carcinoma | |
| Adenocarcinoma | |
| Large cell carcinoma | |
| Non-small carcinoma | |
| Small cell carcinoma | |
| Carcinoid | |
| Unclassified | |
| Other (please specify): | |

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## Further comments

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Name (and title):

Signature:

Date:



Are you a … (please tick below):

| | ✓ |
|---|---|
| Surgeon | |
| Medical Oncologist | |
| Clinical Oncologist | |
| Clinical Nurse Specialist | |
| Other (please specify): | |

**Thank you very much for taking the time to complete this questionnaire.**

**Supplementary File 4: Rules for missing, incomplete, multiple response and out of range data and for calculating intervals**

| |
|---|
| 1. Oversampling/Participation in local screening trials<br>a) To handle oversampling in Ontario, include only the first 315 consecutive lung cancer patients;<br>b) In jurisdictions with no national screen program: exclude patients participated in local screen trials. |
| 2. Language/Participation in study/Presence of cancer<br>Exclude patients who checked "No, I don't understand the language" or "I don't want to participate in this study" or "I don't have cancer". |
| 3. Survey responders<br>a) Exclude Patient/PCP/Specialist survey from the analysis, if it was not written by Patient/PCP/Specialist (example: a medical oncologist completed a PCP survey);<br>b) In the case of duplicates, include only the first survey (example: 2 specialists completed surveys for the same patient). |
| 4. Gender<br>Exclude patients with unknown Gender. |
| 5. Age<br>a) Exclude patients with unknown age;<br>b) Exclude patients younger 40 years;<br>c) Use registry data, if Age is reported by both patient and registry. |
| 6. No cancer or Previous cancer in the same organ<br>a) Exclude patients with no cancer based on registry data;<br>b) Exclude patients with previous cancer in the same organ based on data from registry or free-text for Presentation in the patient survey. |
| 7. Date of consent<br>Exclude patients with date of consent which is unknown, before 01.01.2013 or in the future. |
| 8. Multiple responses to Dates<br>If multiple responses were given to the dates (of first symptom; screening; first presentation to primary care; referral; diagnosis; treatment start), then use the earliest date. |
| 9. Order of Dates<br>The dates must be in the following order –<br>a) First symptom; first presentation to Primary Care; referral; diagnosis; treatment start.<br>b) Screening; diagnosis; treatment start.<br><br>If not, check for mistakes. |
| 10. Date of first symptom<br>Date of first symptom is defined as date of first symptom from patient data. |
| 11. Date of first presentation<br>Date of first presentation to Primary Care is defined as (in the order of declining priority):<br>a) date of first presentation to Primary Care from PCP data;<br>b) date of first presentation to Primary Care and A&E from PCP data; |

c) date of first presentation to Primary Care from patient data.

12. Date of referral

Date of referral is defined as date of referral from PCP data.

13. Date of screening

Date of screening is defined as (in the order of declining priority):

a) date of screening from registry;

b) date of screening from patient data

14. Date of diagnosis

*Definition*

a) If Registry reports both date of histological confirmation and date of confirming investigation, then use date of histological confirmation.
b) Date of diagnosis (based on patient data, PCP data, specialist data, registry data) is defined as (in the order of declining priority):
   - date of diagnosis from registry;
   - date of histological confirmation (from specialist data, PCP data);
   - date of biopsy (from specialist data, PCP data);
   - date of confirming investigation (from specialist data, PCP data);
   - date of first hospital admission (from specialist data, PCP data);
   - date of MDT confirmation (from specialist data, PCP data);
   - date patient was told (from specialist data, PCP data);
   - other date of diagnosis (from specialist data, PCP data, patient data);

Choose a Date from a lower level of hierarchy, if the Date from a higher level is after the Date of consent or more than 9 months (=271 days) before the Date of consent.

*Exclusion criteria*

a) Unknown date of diagnosis;
b) Date of diagnosis is after the date of consent;
c) Date of diagnosis is more than 9 months before the Date of consent.

15. Date of treatment start

a) Date of treatment start from patient data is defined as the earliest of the treatment dates for Surgery, Chemo, Radio and Other;
b) Date of treatment start (based on registry data, specialist data, patient data) is defined as (in the order of declining priority):
   - date of treatment start from registry data,
   - date of treatment start from specialist data,
   - date of treatment start from patient data,
   - anticipated date of treatment from patient data.

16. Imputation of missing day in the date

Imputation rules for missing day (given month and year are known):

a) Set missing day to '16';
b) Consider adjacent dates in a backwards order (from "Treatment" to "First symptom"). For each pair of such adjacent dates: If dates are not in a logical order (e.g.

"Treatment" is before "Diagnosis"), but month and year are the same in both dates, and the day was imputed to '16' in one of the dates:
- Recode the day imputed earlier to '16' to the day from the adjacent date

17. Considering time
If patient gave multiple answers to the "How long did you have symptoms before contacting a doctor?" question, then use the option with the shortest time interval.

18. Delay arranging appointment
If patient gave multiple answers to the "How long did it take to get an appointment with PCP?" question, then use the option with the shortest time interval.

19. Duration of symptoms
If PCP gave multiple answers to the "Duration of symptoms" question, then use the option with the shortest time interval.

20. Definition of Routes to diagnosis

A. *Define Route within a Data Source*

1. Review the free-text for Route (Patient, PCP sources) and re-code, if possible.
2. If PCP reports 'Other' as Route and at least one symptom (or "Duration of Symptoms") or if Patient reports 'Other' as Route and at least one symptom (or date of first symptom or "Consider waiting time" or "Delay arranging appointment"), then re-code the Route in the corresponding data source to 'Other non-screen-detected'-option.
3. In the case of multiple Routes responses (Patient, PCP sources) - use a single option (in the order of declining priority):

a) 'VisitPCP and AE',
b) 'VisitPCP´, 'AE´ (if both 'VisitPCP´ and 'AE´ are given, then re-code as 'VisitPCP and AE'),
c) 'Other non-screen-detected',
d) 'Investigation for another problem' ,
e) 'Other"

*B. Define Route from Alternative Data*

If Route hasn't been reported in either of data sources, then define it 'Other non-screen-detected', if PCP reports at least one symptom (or "Duration of symptoms"); or if Patient reports at least one symptom (or date of first symptom or "Consider waiting time" or "Delay arranging appointment");

C. *Define Route from Data Source Hierarchy*

1. In all jurisdictions, except Sweden – use Route data from (in the order of declining priority):
   a) PCP data;
   b) Patient data;
2. In Sweden – use Route data from Patient data.

21. Patient interval
The Patient interval for non-screen-detected patients is defined as (in the order of declining priority):

a) "Date of first presentation to Primary Care" (rule 11) minus "Date of first symptom" (rule 10);

b) If the interval in (a) is unknown or negative: Calculate the interval as the low boundary of "Considering time" (rule 17) plus the low boundary of "Delay arranging appointment" (rule 18);
c) If the interval in (a) is unknown or negative and the interval in (b) is unknown: Calculate the interval as the low boundary of "Duration of symptoms interval" (rule 19).

22. Primary Care interval
The Primary Care interval for non-screen-detected is defined as "Date of referral" (rule 12) minus "Date of first presentation to Primary Care" (rule 11).

23. Diagnostic interval
a) The Diagnostic interval for non-screen-detected is defined as "Date of diagnosis" (rule 14) minus "Date of first presentation to Primary Care" (rule 11);
b) The Diagnostic interval for screen-detected patients is defined as "Date of diagnosis" (rule 14) minus "Date of screening" (rule 13).

24. Treatment interval
The Treatment interval is defined as "Date of treatment start" (rule 15) minus "Date of diagnosis" (rule 14).

25. Total interval
a) The Total interval for non-screen-detected patients is defined as "Date of treatment start" (rule 15) minus "Date of first symptom" (rule 10);
b) The Total interval for screen-detected patients is defined as "Date of treatment start" (rule 15) minus "Date of screening" (rule 13).

26. Range of Time intervals
The time intervals (Patient, Primary Care, Diagnosis, Treatment, Total) must be in range 0-1 year.
If > 1 year: set the interval to 365 days
If negative: set the interval to 0.

For each jurisdiction calculate the number of imputations due to:

a) unknown day in a date (given known month and year);
b) very large(>1 year) interval;
c) negative interval.

27. Number of visits
If patient gave multiple answers to the "Number of visits" questions, then use the option with a fewer number of visits.

28. Specialist waiting time interval
If patient gave multiple answers to the ""How long did it take to get an appointment with specialist?" question, then use the option with the shortest time interval.

29. Type of treatment
If patient ticked both "Yes" and "No" as answers to the "Type of treatment (Surgery, Chemotherapy, Radiotherapy)" questions, then choose "Yes" answer.

30. Health state
If patient gave multiple answers to the “Health state” question, then use the option with a better health condition.

31. Comorbidity
a) If patient ticked both “Yes” and “No” as answers to the “Comorbidity (Heart disease, Stroke, Lung disease, Diabetes)” questions, then choose “Yes” answer;
b) If both patient and PCP report “Comorbidity”, then use the PCP Data.

32. Ethnicity
a) If patient didn’t report “Ethnicity”, then use the information from (in the order of declining priority):
- “Ethnicity_Other_Details”;
- “Other main language spoken at home”;
- “The main language spoken at home” (only for Victoria);
- “The main language spoken at home is the chief one for this jurisdiction”=”Yes” given
“Main language spoken at home is other than the main one for this jurisdiction”=”No”;

b) Consider Ethnicity as unknown, if answers to the “Ethnicity” question are multiple and belong to different categories ( ‘white’, ‘Asian’, ‘black’, ‘other’).

33. Education
If patient gave multiple answers to the “Education” question, then use the option with a higher level of education.

34. Smoking Current
a) If patient ticked both “Yes” and “No” as answers to the “Smoking Current” question, then use “Yes” answer;
b) If patient hasn’t ticked neither “Yes” nor “No, then consider this case as Unknown.

35. Smoking Number
If patient reports “SmokingNumber” as text, then re-code using following rules:
a) Where there is a number smoked /day – accept number;
b) Where a range has been given – take the upper value;
c) Where patient has put 10+ or 20+ - capture this as 11 or 21;
d) Where number of cigarettes smoked in the past and currently being smoked are provided - average the numbers;
e) Non entries code as “.” ;
f) Non-smokers (eg, “nil”, “N/A“) are coded as “0”.

36. Smoked ever
a) If patient ticked both “Yes” and “No” as answers to the “Smoking ever” question, then use “Yes” answer;
b) If patient hasn’t ticked neither “Yes” nor “No”: consider it as “Yes”, if patient is a current smoker (“Smoking_Current=”Yes””) or has specified a number of cigarettes (“SmokingNumber”>0). Otherwise consider this case as Unknown.
c) If patient has ticked “No”: recode it to “Yes”, if patient is a current smoker (“Smoking_Current=”Yes”).

37. Nature of referral
    a) Review free-text for "Nature of referral" (PCP Data) and re-code, if possible;
    b) In the case of multiple responses, use a single option as (in the order of declining priority):

        - "Referral for immediate admission";
        - "Urgent referral";
        - "Less urgent referral";
        - "General referral" ;
        - "No referral";
        - "Other".

38. Refer Public or Private
    a) If PCP ticked both "Public" and "Private" as answers to the "Refer Public or Private" question, then use "Private" answer;
    b) If PCP hasn't ticked neither "Public" nor "Private", then consider this case as Unknown.

39. Type of referral
    If specialist gave multiple responses to the "How was the patient referred…" question, then use a single option (in the order of declining priority):

        - "Screening";
        - "Respiratory clinic";
        - "General surgery clinic";
        - "General gynaecology";
        - "Specialist/consultant";
        - "PCP";
        - "Other".

40. First Attendance Place
    If specialist gave multiple responses to the "First Attendance Place" question, then consider this case as Unknown.

41. Stage-TNM
    a) If specialist gave multiple responses to the "Stage_TNM" question, then use the highest category;
    b) If registry gave multiple responses to the "Stage_TNM", then use a single option (in the order of declining priority):
        - stage at time of diagnosis
        - stage at surgery
        - stage at oncology
    c) If "Stage_TNM" is reported by both the specialist and registry, then use the registry data.

## Supplementary File 5 - Tables

**Table 1:** Classification of symptoms reported by patients into cancer specific and non-cancer specific

| Cancer specific symptoms |
|---|
| 1 persistent cough |
| 2 chest infection that wouldn't get better |
| 3 coughing up blood-stained phlegm (sputum) |
| 4 breathlessness |
| 5 chest or shoulder pain |
| 6 a hoarse voice |
| 7 difficulty swallowing |
| 8 swelling of lymph nodes (glands) in my neck |
| 9 ends of fingers becoming larger |
| 10 breast and axilla swelling (in men) |

| Non-cancer specific symptoms |
|---|
| 1 a dull ache or sharp pain when I coughed or took a deep breath |
| 2 pain/discomfort under my ribs |
| 3 face swelling |
| 4 blood clots (thrombosis) |
| 5 pins and needles or numbness in fingers |
| 6 weight loss |
| 7 felt sick/vomiting/nausea/loss of appetite |
| 8 fatigue |
| 9 muscle weakness |
| 10 drowsiness, weakness, dizziness or confusion |
| 11 high temperature (fever) of 38°C (100.4°F) |
| 12 other |

**Table 2:** Time intervals (days) depicted as median (50th), 75th and 90th percentiles for each of the ten jurisdictions. In Sweden, no data was available on primary care interval

| Intervals | Centiles | Wales | Denmark | Sweden | England | N Ireland | Scotland | Manitoba | Ontario | Norway | Victoria |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient Interval | Number | 181 | 233 | 172 | 213 | 179 | 169 | 133 | 205 | 55 | 141 |
| | Median | 21 | 14 | 21 | 17 | 18 | 21 | 25 | 22 | 19 | 14 |
| | 75th centile | 61 | 53 | 61 | 65 | 60 | 60 | 67 | 61 | 60 | 60 |
| | 90th centile | 216 | 180 | 214 | 205 | 240 | 267 | 180 | 187 | 277 | 180 |
| Primary Care interval | Number | 110 | 159 | n/a | 147 | 124 | 119 | 80 | 75 | 19 | 89 |
| | Median | 20 | 7 | | 11 | 13 | 16 | 30 | 29 | 7 | 10 |
| | 75th centile | 43 | 20 | | 31 | 51 | 35 | 75 | 73 | 41 | 36 |
| | 90th centile | 91 | 64 | | 73 | 112 | 90 | 138 | 183 | 102 | 99 |
| Diagnostic interval | Number | 176 | 229 | 165 | 212 | 170 | 173 | 138 | 212 | 52 | 160 |
| | Median | 45 | 35 | 28 | 54 | 65 | 42 | 87 | 57 | 51 | 54 |
| | 75th centile | 108 | 67 | 83 | 100 | 122 | 106 | 147 | 122 | 109 | 106 |
| | 90th centile | 162 | 162 | 143 | 161 | 281 | 198 | 265 | 331 | 160 | 240 |
| Treatment interval | Number | 192 | 279 | 190 | 238 | 200 | 187 | 182 | 263 | 87 | 199 |
| | Median | 43 | 16 | 34 | 22 | 32 | 42 | 19 | 47 | 24 | 0 |
| | 75th centile | 64 | 25 | 59 | 41 | 48 | 62 | 56 | 70 | 44 | 22 |
| | 90th centile | 89 | 37 | 77 | 56 | 72 | 90 | 97 | 96 | 72 | 41 |
| Total interval | Number | 147 | 192 | 147 | 176 | 157 | 143 | 117 | 178 | 52 | 113 |
| | Median | 116 | 67 | 107 | 114 | 105 | 117 | 127 | 130 | 79 | 78 |
| | 75th centile | 204 | 116 | 190 | 183 | 227 | 253 | 216 | 216 | 186 | 195 |
| | 90th centile | 365 | 210 | 329 | 323 | 365 | 365 | 365 | 339 | 271 | 355 |

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**The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.**

| | Item No. | STROBE items | Location in manuscript where items are reported | RECORD items | Location in manuscript where items are reported |
|---|---|---|---|---|---|
| **Title and abstract** | | | | | |
| | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found | Title and abstract – p 1 and 3 | RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.<br><br>RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.<br><br>RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract. | Abstract – p 3<br><br>Abstract – p 3<br><br>N/A |
| **Introduction** | | | | | |
| Background rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Introduction – p 6 | | |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Introduction – p 6 | | |
| **Methods** | | | | | |
| Study Design | 4 | Present key elements of study design early in the paper | Methods – p 6 | | |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Methods – p 6-8 | | |
| Participants | 6 | *(a) Cohort study* - Give the eligibility criteria, and the | Methods – p 6 – and as reference to | RECORD 6.1: The methods of study population selection (such as codes or | Provided as reference to |

| | | | | | |
|---|---|---|---|---|---|
| | | sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants<br><br>*(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study* - For matched studies, give matching criteria and the number of controls per case | previous paper.<br><br>N/A | algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.<br><br>RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.<br><br>RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage. | previous paper.<br><br>Provided as appendix and in reference to previous paper.<br><br>N/A |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. | Methods – p 6-9 – and as reference to previous paper. | RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided. | N/A |
| Data sources/ measurement | 8 | For each variable of interest, give sources of data and details of methods of assessment (measurement).<br>Describe comparability of assessment methods if there is more than one group | Methods – p 6-9 – and as reference to previous paper. | | |
| Bias | 9 | Describe any efforts to address potential sources of bias | Methods – p 7-8, discussion – p 24-25 – and as reference to | | |

| | | | | | |
|---|---|---|---|---|---|
| | | | previous paper. | | |
| Study size | 10 | Explain how the study size was arrived at | Methods – p 6 – and as reference to previous paper. | | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | Methods – p 6-8 – and as reference to previous paper. | | |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding<br>(b) Describe any methods used to examine subgroups and interactions<br>(c) Explain how missing data were addressed<br>(d) *Cohort study* - If applicable, explain how loss to follow-up was addressed<br>*Case-control study* - If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy<br>(e) Describe any sensitivity analyses | Methods – p 8 – and as reference to previous paper. | | |
| Data access and cleaning methods | | .. | | RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. | N/A |

| | | | | | |
|---|---|---|---|---|---|
| | | | | RECORD 12.2: Authors should provide information on the data cleaning methods used in the study. | Methods – p 7 |
| Linkage | | .. | | RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided. | N/A |
| **Results** | | | | | |
| Participants | 13 | (a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed)<br>(b) Give reasons for non-participation at each stage.<br>(c) Consider use of a flow diagram | Results and as table – p 10-11. Flow diagram in previous paper, referenced. | RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram. | Results – p 10-15 - and as table. Flow diagram in previous paper, referenced. |
| Descriptive data | 14 | (a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate the number of participants with missing data for each variable of interest<br>(c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount) | Results and as table – p 10-15. | | |
| Outcome data | 15 | *Cohort study* - Report numbers of outcome events or summary measures over time<br>*Case-control study* - Report numbers in each exposure category, or summary measures | Results and as table – p 16-23. | | |

| | | | | | |
|---|---|---|---|---|---|
| | | of exposure<br>*Cross-sectional study* - Report numbers of outcome events or summary measures | | | |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(b) Report category boundaries when continuous variables were categorized<br>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Results and as table – p 21-23. | | |
| Other analyses | 17 | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses | Results – p 23. | | |
| **Discussion** | | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | Discussion – p 24 | | |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Discussion – p24-25 | RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported. | Discussion – p24-25 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar | Discussion – p25-28 | | |

| | | | | | |
|---|---|---|---|---|---|
| | | studies, and other relevant evidence | | | |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | Discussion, conclusion – p25-29. | | |
| **Other Information** | | | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Funding statement – p 31 | | |
| Accessibility of protocol, raw data, and programming code | | .. | | RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code. | Availability of data and material statement – p 31 |

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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# Time intervals and routes to diagnosis for lung cancer in ten jurisdictions: cross-sectional study findings from the International Cancer Benchmarking Partnership (ICBP)



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| | |

**Time intervals and routes to diagnosis for lung cancer in ten jurisdictions: cross-sectional study findings from the International Cancer Benchmarking Partnership (ICBP)**

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Word count: 3074; Tables: 6 ; Figures: 2 ; Appendix A-D

## Abstract

### Objective

Differences in time intervals to diagnosis and treatment between jurisdictions may contribute to previously reported differences in stage at diagnosis and survival. The International Cancer Benchmarking Partnership Module 4 (ICBP M4) reports the first international comparison of routes to diagnosis and time intervals from symptom onset until treatment start for lung cancer patients.

### Design

Newly diagnosed lung cancer patients, their primary care physicians (PCP) and cancer treatment specialists (CTS) were surveyed in Victoria (Australia), Manitoba and Ontario (Canada), Northern Ireland, England, Scotland and Wales (UK), Denmark, Norway and Sweden. Using Wales as the reference jurisdiction, the 50$^{th}$, 75$^{th}$ and 90$^{th}$ percentiles for intervals were compared using quantile regression adjusted for age, gender and comorbidity.

### Participants

Consecutive newly diagnosed lung cancer patients, aged >40 years, diagnosed between October 2012 and March 2015 were identified through cancer registries. Of 10,203 eligible symptomatic patients contacted, 2,631 (27.5%) responded and 2,143 (21.0%) were included in the analysis. Data was also available from 1,211 (56.6%) of their PCPs and 643 (37.0%) of their CTS.

### Primary and secondary outcome measures:

Interval lengths (days, primary), routes to diagnosis, symptoms (secondary).

### Results

With the exception of Denmark (-49 days), in all other jurisdictions the median adjusted total interval from symptom onset to treatment, for respondents diagnosed in 2012-15, was similar to that of Wales (116 days). Denmark had shorter median adjusted primary care interval (-11 days) than Wales (20 days); Sweden had shorter (-20) and Manitoba longer (+40) median adjusted diagnostic intervals compared to Wales (45 days). Denmark (-13), Manitoba (-11), England (-9) and Northern Ireland (-4) had shorter median adjusted treatment intervals than Wales (43 days). The differences were greater for the 10% of patients who waited the longest. Based on overall trends, jurisdictions could be grouped into those with trends of reduced,

longer and similar intervals to Wales.The proportion of patients diagnosed following presentation to the PCP ranged from 35-75%.

**Conclusion**

There are differences between jurisdictions in interval to treatment, which are magnified in lung cancer patients who wait the longest. The data could help jurisdictions develop more focused lung cancer policy and targeted clinical initiatives. Future analysis will explore if these differences in intervals impact on stage or survival.

**Key words:**

lung cancer, routes to diagnosis, time intervals, international health systems, symptomatic presentation

**Strengths and limitations of this study**

- This is the first study to use standardized survey methods and definitions to systematically examine key intervals from patients first noticing symptoms or bodily changes until the start of treatment for lung cancer across multiple jurisdictions
- Recall bias was minimised by the triangulation of different data sources and by patients completing the questionnaire within a limited time window (median 5 months) after the cancer diagnosis
- A key limitation, as with all questionnaire-based studies was selection and non-response bias which varied across jurisdictions
- Recruitment of patients up to 9 rather than 6 months after diagnosis might have magnified selection bias due to high mortality in lung cancer but a sensitivity analysis suggests that this did not impact on the results.
- The comparisons for Norway and Victoria, are limited by small sample size and inclusion of only surgical patients, respectively.

## Introduction

Lung cancer is the most common cancer worldwide, with nearly 1.83 million cases diagnosed in 2012, and is the leading cause of cancer death globally, accounting for 19% of cancer deaths.[1] Survival is typically low, with 5-year survival in Europe,North America and Australia <20%.[2-3] A key factor is diagnosis at advanced stage. Reasons for this are multi-faceted and include delays due to the atypical nature of some presenting symptoms, poor sensitivity of chest X-rays and physicians not acting quickly enough.[4] Within European countries, differences of 12 and 5 percentage points in 1- and 5-year relative survival, respectively, have been reported for lung cancers diagnosed between 1999-2007.[5] This and other international comparisons raises the possibility of additional contributory factors such as variations in referral patterns, access to diagnostic tests and delays in treatment.[6]

One way of addressing this is to chart the patient journey from first noticing symptoms to treatment start. Many national studies using different methodologies have reported on time intervals to treatment of lung cancer and there are reviews that have looked at international timeframe comparisons [7-10].[11-24] However, as far as we are aware there is no study that has undertaken international comparisons of timeliness across multiple countries using the same methodology.

The International Cancer Benchmarking Partnership (ICBP) was established to explore differences in cancer outcomes and their causes in countries with comparable wealth and universal access to healthcare.[25] We report results from Module 4 (ICBP M4) on differences in time intervals and routes to diagnosis in symptomatic lung cancer patients from ten jurisdictions in Australia, Canada, Denmark, Norway, Sweden and the United Kingdom.

## Methods

Methods have been previously detailed.[26] In brief, in each of the ten participating jurisdictions (Victoria (Australia), Manitoba, Ontario (Canada), Denmark, Norway, Sweden Northern Ireland, England, Scotland and Wales), consecutive patients aged ≥40 years, newly diagnosed with malignant lung or bronchus cancer (ICD-10:C34.0-C34.9; ICD-O-3 behaviour code /3) were identified by the cancer registry using validated methods (hospital episode, cancer registration, pathology). Exclusion criteria included previous lung or synchronous cancers. Patients with a previous non-lung primary cancer were eligible. Target recruitment was 200 symptomatic patients per jurisdiction.

Following a vital status check, cancer registries posted the patient questionnaire (Appendix A1) either 1) to the relevant primary care physician (PCP) who then forwarded the pre-

addressed envelope to the patient after confirmation that the person was aware of the diagnosis and not deemed too sick/anxious to participate in the survey. (Wales, England, Scotland) or 2) to the patient directly or via the research team (remaining seven jurisdictions). In an attempt to decrease attrition and recall bias, the protocol initially specified that all patient questionnaires should be completed within 6 months of diagnosis. As there were administrative delays in cancer notification, this was extended to 9 months.

On receipt of a completed patient questionnaire, in all jurisdictions except Sweden, the relevant PCP and cancer treatment specialist (CTS) were sent questionnaires (Appendix A.2 and A.3). Specialists provided information on diagnosis and start date of treatment. The latter was collected directly from registry records in Northern Ireland and clinical databases in Denmark. Manitoba did not provide specialist data. Date of diagnosis and stage was also collected where possible through cancer registries. Information on the types of treatment (surgery, chemotherapy, radiotherapy and other) were obtained from the patient survey.

*Data handling*

Data were recoded centrally to ensure that the same explicit rules were applied throughout. Patients in whom age, date of diagnosis or consent were missing were excluded from analyses. Rules were used to combine data from the different sources in a standardised way that ensured reproducibility and transparency (Appendix B). The rules employed a 'hierarchy' principle in terms of the order in which different data sources were used and included imputation rules based on the available data. The exact rule was guided by the measure in question – for example, patient interval was collected primarily from the patient questionnaire whereas primary care time-points from the PCP questionnaire. We applied rules for outliers and implausible measures (e.g. negative time intervals were recorded to zero-days and intervals longer than a year to 365 days).

*Routes to diagnosis and symptoms prompting physician visit*

These were derived from patient and PCP responses. Symptoms were coded by two PCP authors (DW and PV) into 'lung cancer specific' or 'other' (Appendix C1).

*Time intervals*

Time intervals were derived using the checklist for the Aarhus Statement.[27] The following time-points were used to calculate the corresponding time intervals (Figure 1):

- first noticing symptoms
- first presentation to health care
- first referral to secondary care

- diagnosis date
- start of curative or palliative treatment

FIGURE 1

All time-points were validated if there were obvious inconsistencies and negative intervals were set to 0 days. All intervals were truncated at 365 days. Missing data were imputed based on specific rules to ensure that the direction of a possible misclassification bias was known.

*Demographics*

Health status was measured using the self-reported general health item from short form 36 health survey (SF36).[28] Comorbidity was defined as one of four patient or PCP-reported diseases (heart or lung disease, stroke or diabetes) and categorised into: 'none', 'medium' (one or two) or 'high' (three or four). Level of educational was categorised as 'low' (vocational school or lower) and 'high' (university). Stage data (tumour, node, metastasis - TNM - classification) was grouped as I, II, III, IV or missing.[29]

*Statistical analysis*

Patient characteristics across jurisdictions were compared using Kruskal-Wallis test for continuous and ordinal data. For nominal data we used Pearson's chi-squared test and Fisher's exact test (if more than 20% of expected cell counts were less than 5 or at least one expected cell count was 0). The differences in intervals between the jurisdictions were estimated using quantile regression, as this method allows for a comparison across the whole distribution of length of the interval.[30] As we were interested in a measure of central tendency of length of the interval and in long and very long intervals, the focus of the study was on the $50^{th}$(median), $75^{th}$ and $90^{th}$ interval percentiles. Wales was chosen as the reference jurisdiction as it had the lowest lung cancer survival in ICBP Module 1 analysis.[10] Since the length of the interval in days is a continuous measure which has been rounded, we applied the quantile regression analysis on the smoothed quantiles; the method based on the smoothed quantiles is recommended for analyses of discrete (count) data [31]. In STATA this method is implemented in the 'qcount' procedure.[32] Parameters were calculated with 1000 jittered samples. For all interval analyses, the differences in intervals were calculated as marginal effects after quantile regression by setting the continuous covariate (age) to their mean values and the categorical covariates (sex and comorbidity) to their modes. Significance level was set to $\leq 0.05$ with 95% confidence intervals (95%CI) calculated where appropriate. Statistical analyses were carried out using STATA v14.

*Sensitivity and validity analyses*

All analyses were repeated using only (1) those who fulfilled the 6-month cut-off criteria for interval from diagnosis to questionnaire completion and (2) patient data. The effect of excluding patients for whom at least one interval was missing was investigated.We also repeated the analysis after omitting time intervals which were negative or over 365 days. Agreement between the different data sources (registry, patient, PCP (except in Sweden) and CTS (except in Sweden and Manitoba) was measured by Lin's concordance correlation coefficient (CCC).[33]

*Patient involvement*

The research questions for this survey drew on an extensive literature relating to diagnosis and treatment delays leading to negative patient experiences. While patient experience was not a primary outcome measure for this study, patients were given the opportunity to comment on their experience through questionnaire free-text response options (under separate analysis). Patients were involved in the piloting of study instruments to ascertain if recruitment and questionnaire content and dissemination strategies were appropriate, described elsewhere.[26] Each jurisdiction has committed to communicating the findings and local implications of this study to organisations representing their study participants.

**Results**

Of 14,583 lung cancer patients, diagnosed between October 2012 and March 2015 who were alive when identified, 70% (10,203/14,583) were contacted (Table 1). Of 4380 not contacted, 3367 (77%) were from England, Wales and Scotland. Major reasons reported by the PCP for not forwarding the survey included patients being terminally ill, not aware of cancer diagnosis at the time of request, having cognitive or visual impairment, language / communication difficulties, no longer at the address, not wishing to take part in research and a handful not having the index cancer. In addition patents identified were not contacted in England as the target recruitment had been exceeded. For the non-UK jurisdictions, the main reasons for not contacting patients were the patient having died or no longer at the address.

2,631 (27.5% of contacted, 18% of eligible) completed the patient questionnaire at a median of 5 months (range: 0.1,9) after diagnosis (Table 2). The response rate of contacted patients varied from 11.1% (146/1318) in Norway to 61.8% (333/539) in Denmark. Responding patients were more likely to be aged 60-79 years with less advanced stage (Table 1) and alive one year post diagnosis (data not shown). Of the 2,631 responses, 2,143 (81.5%) were included in the analyses which equates to 14.7% (2,143/14,583) of eligible patients. The key reason respondents were excluded were local oversampling (43.9%; 214/488) for additional analyses

(Table 1). In Victoria, the registry was only able to contact patients who had undergone surgery while the sample size in Norway was limited (n=88) due to delays in securing appropriate approvals.

**Table 1:** Cohort for all ten jurisdictions and overall

| Jurisdiction | Patients approached via PCP | | | | | | Patient approached directly by registries/research teams | | | | | | | | | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Wales | | England | | Scotland | | N Ireland | | Denmark | | Manitoba | | Ontario | | Sweden | | Norway | | Victoria | | | |
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| **Eligible patients** [a, b] | **1,811** | **(100)** | **2,517** | **(100)** | **1,366** | **(100)** | **620** | **(100)** | **539** | **(100)** | **980** | **(100)** | **4,080** | **(100)** | **493** | **(100)** | **1,318** | **(100)** | **859** | **(100)** | **14,583** | **(100)** |
| **Packs sent to PCP** [c, d] | **1,811** | **(99.7)** | **1,759** | **(69.9)** | **1,137** | **(83.2)** | | | | | | | | | | | | | | | **4,707** | **(82.7)** |
| pack not forwarded by PCP | 547 | (30.1) | 255 | (14.5) | 201 | (17.7) | | | | | | | | | | | | | | | 1,003 | (21.3) |
| unsure if pack forwarded by PCP | 531 | (29.2) | 559 | (31.8) | 234 | (20.6) | | | | | | | | | | | | | | | 1,324 | (28.1) |
| **Patients contacted by PCP** [c, d] | **733** | **(40.4)** | **945** | **(53.7)** | **702** | **(61.7)** | | | | | | | | | | | | | | | **2,380** | **(50.6)** |
| **Patients approached directly** [c] | | | | | | | **614** | **(99.0)** | **539** | **(100)** | **745** | **(76.0)** | **3,687** | **(90.4)** | **493** | **(100)** | **1,200** | **(91)** | **545** | **(63.4)** | **7,823** | **(88)** |
| patient died | | | | | | | 6 | (1.0) | 0 | (0.0) | 103 | (13.8) | 249 | (6.8) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 358 | (4.6) |
| no address | | | | | | | 0 | (0.0) | 0 | (0.0) | 9 | (1.2) | 255 | (6.9) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 264 | (3.4) |
| Other | | | | | | | 0 | (0.0) | 0 | (0.0) | 6 | (0.8) | 215 | (5.8) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 221 | (2.8) |
| **Patient responses (% of eligible patients)**[c] | **223** | **(12.3)** | **261** | **(10.4)** | **235** | **(17.2)** | **226** | **(36.5)** | **333** | **(61.8)** | **205** | **(20.9)** | **572** | **(14.0)** | **217** | **(44)** | **146** | **(11.1)** | **213** | **(24.8)** | **2,631** | **(18)** |
| **Patient responses (% of contacted)**[e] | **223** | **(30.4)** | **261** | **(27.6)** | **235** | **(33.5)** | **226** | **(37.2)** | **333** | **(61.8)** | **205** | **(32.7)** | **572** | **(19.3)** | **217** | **(44)** | **146** | **(12.2)** | **213** | **(39.1)** | **2,631** | **(27.5)** |
| extra sample for local purpose | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 214 | (37.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 214 | (8.1) |
| other | 0 | (0.0) | 0 | (0.0) | 35 | (14.9) | 25 | (11.1) | 38 | (11.4) | 0 | (0.0) | 43 | (7.5) | 0 | (0.0) | 0 | (0.0) | 3 | (1.4) | 144 | (5.5) |
| **Patient surveys submitted for analyses** [f] | **223** | **(100)** | **261** | **(100)** | **200** | **(85.1)** | **201** | **(88.9)** | **295** | **(88.6)** | **205** | **(100)** | **315** | **(55.1)** | **217** | **(100)** | **146** | **(100)** | **210** | **(98.6)** | **2,273** | **(86.4)** |
| excluded for analyses – total | 12 | (5.4) | 9 | (3.4) | 2 | (1.0) | 1 | (0.5) | 10 | (3.4) | 3 | (1.5) | 27 | (8.6) | 6 | (2.8) | 58 | (39.7) | 2 | (1.0) | 130 | (5.7) |
| - previous cancer | 0 | (0.0) | 5 | (1.9) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 3 | (1.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 8 | (0.4) |
| - unknown date of consent or diagnosis | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 5 | (1.7) | 0 | (0.0) | 1 | (0.3) | 6 | (2.8) | 4 | (2.7) | 0 | (0.0) | 16 | (0.7) |
| - consent too late/too early | 12 | (5.4) | 4 | (1.5) | 2 | (1.0) | 1 | (0.5) | 5 | (1.7) | 3 | (1.5) | 22 | (7.0) | 0 | (0.0) | 33 | (22.6) | 2 | (1.0) | 84 | (3.7) |
| - other | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) | 0 | (0.0) | 21 | (14.4) | 0 | (0.0 | 22 | (1.0) |
| **Patients included in analyses** [i] **(% of forwarded surveys)** | **211** | **(94.6)** | **252** | **(96.6)** | **198** | **(99.0)** | **200** | **(99.5)** | **285** | **(96.6)** | **202** | **(98.5)** | **288** | **(91.4)** | **211** | **(97.2)** | **88** | **(60.3)** | **208** | **(99.0)** | **2,143** | **(94.3)**[h] |
| **PCP surveys** [j] **(% of analysed patients)** | **133** | **(63.0)** | **196** | **(77.8)** | **149** | **(75.3)** | **181** | **(90.5)** | **218** | **(76.5)** | **109** | **(54.0)** | **93** | **(32.5)** | **n/a** [h] | | **27** | **(30.7)** | **105** | **(50.5)** | **1,211** | **(56.6)**[i] |
| **Specialist surveys** [k] **(% of analysed patients)** | **98** | **(46.4)** | **153** | **(60.7)** | **106** | **(53.5)** | **n/a** [g] | | **149** [g] | **(52.3)** | **n/a** [h] | | **62** | **(21.7)** | **n/a** [h] | | **20** | **(22.7)** | **55** | **(26.4)** | **643** | **(37.0)**[m] |

[a]Eligible as per protocol: individual aged 40 years or more, with cancer of the lung or bronchus (ICD-10 code: C34.0-C34.9; behaviour code ICD-O 3) but no synchronous primary cancer or prior history of lung cancer, alive at identification who completed consent to participate within nine months of diagnosis. [b]In some jurisdictions some 'eligible' patients had pre-opted out from being contacted and a small number where PCP information was not available. [c]Percentages of eligible patients. [d]Maximum of potentially contacted patients. i.e. sum of packs forwarded by PCP and packs unsure if forwarded by PCP. [e]Percentages of patients contacted by PCP (see note d) for Wales, England and Scotland or percentages of patients contacted directly by a registry; excl. non-accessible patients due to death or no patient addresses (all other jurisdictions). [f]Percentages of patient responses. [g]Data obtained from registries instead in N Ireland and Denmark. [h]Data not collected in this jurisdiction. [i]Denominator = total number of forwarded cases excl. patients not included in analytic sample in Ontario. [j]Denominator r = total number of analysed cases excl. patients from Sweden. [k]Denominator = total number of analysed cases excl. patients from Sweden. Manitoba & N Ireland

*Baseline characteristics*

Patient characteristics are detailed in Table 2. The cohort was predominantly White (95%), median age 70 years (IQR 64,75) with 82% reporting 'low' levels of education. Norway provided stage data classified as local, regional and distant which could not be converted to TNM stage data.

Ontario was the only jurisdiction with more female (65%) than male respondents. While self-reported health differed significantly, with Welsh patients (9%) reporting twice as high 'poor health' rates than English or Swedish (4%) and eight-fold that of Manitoba (2%), there was no difference in self-reported comorbidity rates. Even after the exclusion of Victoria, there was significant variation in early Stage (I/II) disease which ranged from 25% (Wales) to 59% (Ontario) and surgical resection rates which varied from 27% (Wales) to 58% (Ontario) (Table 2).

**Table 2.** The characteristics of eligible patients by jurisdictions and overall

| | Wales (N=211) | England (N=252) | Scotland (N=198) | N Ireland (N=200) | Denmark (N=285) | Manitoba (N=202) | Ontario (N=288) | Sweden (N=211) | Norway (N=88) | Victoria (N=208) | Overall (N=2143) | p-value[6] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Date of diagnosis of first patient | 03/04/2013 | 28/01/2013 | 26/04/2013 | 22/01/2013 | 16/05/2013 | 10/10/2012 | 08/10/2013 | 01/10/2013 | 16/01/2014 | 08/01/2013 | 10/10/2012 | |
| Date of diagnosis of last patient | 25/09/2014 | 14/08/2013 | 04/12/2013 | 02/12/2014 | 13/11/2013 | 27/03/2015 | 01/10/2014 | 30/05/2014 | 21/01/2015 | 28/12/2014 | 27/03/2015 | |
| Interval from diagnosis date of first patient to last patient in months (recruitment period) | 18 | 7 | 7 | 23 | 6 | 30 | 12 | 8 | 12 | 24 | 30 | |
| Median (range) interval diagnosis to questionnaire completion in months | 5 (0.6,9) | 5 (3,9) | 5 (1,9) | 4 (0.1,9) | 5 (2,8) | 6 (4,9) | 6 (4,9) | 4 (3,8) | 7 (5,9) | 5 (0.2,8) | 5 (0.1,9) | |
| **Age** years Median (IQR) | 71 (65, 77) | 71 (65, 77) | 70 (64, 76) | 69 (62, 75) | 70 (63, 74) | 70 (63, 77) | 70 (64, 75) | 70 (63, 75) | 69 (64, 73) | 68 (63, 73) | 70 (64, 75) | 0.010[1] |
| **Sex** n(%) Male | 127(60) | 134(53) | 100(51) | 105(53) | 151(53) | 100(50) | 131(45) | 111(53) | 46(52) | 112(54) | 1117(52) | 0.159[2] |
| **Health State** n(%) Good | 135(64) | 176(70) | 131(66) | 126(63) | 190(67) | 156(77) | 220(76) | 152(72) | 50(57) | 163(78) | 1499(70) | <0.001*[1] <0.001**[2] |
| Fair | 55(26) | 59(23) | 52(26) | 51(26) | 62(22) | 41(20) | 47(16) | 49(23) | 32(36) | 33(16) | 481(22) | |
| Poor | 20(9) | 11(4) | 14(7) | 16(8) | 18(6) | 4(2) | 16(6) | 9(4) | 6(7) | 10(5) | 124(6) | |
| Missing | 1(0.5) | 6(2) | 1(0,5) | 7(4) | 15(5) | 1(0.5) | 5(2) | 1(0.5) | 0(0) | 2(1) | 39(2) | |
| **Comorbidity**[3] n(%) No | 92(44) | 113(45) | 98(49) | 82(41) | 111(39) | 101(50) | 136(47) | 114(54) | 35(40) | 98(47) | 980(46) | 0.029*[1] 0.032**[2] |
| Medium | 111(53) | 129(51) | 92(46) | 103(52) | 157(55) | 93(46) | 132(46) | 87(41) | 48(55) | 100(48) | 1052(49) | |
| High | 7(3) | 9(4) | 8(4) | 15(8) | 11(4) | 6(3) | 18(6) | 6(3) | 5(6) | 8(4) | 93(4) | |
| Missing | 1(0.5) | 1(0.4) | 0(0) | 0(0) | 6(2) | 2(1) | 2(0.7) | 4(2) | 0(0) | 2(1) | 18(0.8) | |
| **Education** n(%) Low | 172(82) | 217(86) | 174(88) | 166(83) | 232(81) | 170(84) | 224(78) | 159(75) | 65(74) | 181(87) | 1760(82) | <0.001*[1] <0.001**[2] |
| High | 11(5) | 15(6) | 11(6) | 17(9) | 15(5) | 21(10) | 55(19) | 48(23) | 14(16) | 24(12) | 231(11) | |

| | Wales (N=211) | England (N=252) | Scotland (N=198) | N Ireland (N=200) | Denmark (N=285) | Manitoba (N=202) | Ontario (N=288) | Sweden (N=211) | Norway (N=88) | Victoria (N=208) | Overall (N=2143) | p-value[6] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Missing | 28(13) | 20(8) | 13(7) | 17(9) | 38(13) | 11(5) | 9(3) | 4(2) | 9(10) | 3(1) | 152(7) | |
| **Ethnicity** n(%) White | 205(97) | 249(99) | 197(99) | 196(98) | 267(94) | 173(86) | 261(91) | n/a | 87(99) | 199(96) | 1834(95) | <0.001*[2] <0.001**[2] |
| Asian | 1(0.5) | 0(0) | 1(0.5) | 0(0) | 0(0) | 12(6) | 21(7) | n/a | 1(1) | 6(3) | 41(2) | |
| Black | 0(0) | 1(0.4) | 0(0) | 0(0) | 1(0.4) | 0(0) | 1(0.3) | n/a | 0(0) | 0(0) | 3(0.2) | |
| Other | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 15(7) | 2(0.7) | n/a | 0(0) | 0(0) | 17(0.9) | |
| Missing | 5(2) | 2(0.8) | 0(0) | 4(2) | 17(6) | 2(1) | 3(1) | n/a | 0(0) | 3(1) | 36(2) | |
| **Smoking** n(%) Never | 13(6) | 18(7) | 12(6) | 19(10) | 15(5) | 22(11) | 31(11) | 41(19) | 11(13) | 33(16) | 215(10) | <0.001*[2] <0.001**[2] |
| Currently | 19(9) | 28811) | 26(13) | 41(21) | 58(20) | 24(12) | 29(10) | 29(14) | 11(13) | 9(4) | 274(13) | |
| In the past | 174(82) | 204(81) | 160(81) | 137(69) | 205(72) | 156(77) | 225(78) | 139(66) | 66(75) | 165(79) | 1631(76) | |
| Missing | 5(2) | 2(0.8) | 0(0) | 3(2) | 7(2) | 0(0) | 3(1) | 2(0.9) | 0(0) | 1(0.5) | 23(1) | |
| **Tumour stage – TNM** n(%) I | 26(12) | 68(27) | 49(25) | 42(21) | 74(26) | 83(41) | 133(46) | 59(28) | 3(3) | 124(60) | 661(31) | <0.001*[1] <0.001**[2] |
| II | 27(13) | 36(14) | 32(16) | 33(17) | 26(9) | 19(9) | 38(13) | 11(5) | 5(6) | 47(23) | 274(13) | |
| III | 64(30) | 57(23) | 56(28) | 59(30) | 84(29) | 48(24) | 54(19) | 40(19) | 5(6) | 19(9) | 486(23) | |
| IV | 62(29) | 80(32) | 50(25) | 62(31) | 94(33) | 48(24) | 54(19) | 94(45) | 3(3) | 13(6) | 560(26) | |
| Missing | 32(15) | 11(4) | 11(6) | 4(2) | 7(2) | 4(2) | 9(3) | 7(3) | 72(82)[4] | 5(2) | 162(8) | |
| **Tumour stage – TNM**[5] n(%) I/II | 53(25) | 104(41) | 81(41) | 75(38) | 100(35) | 102(51) | 171(59) | 70(33) | 8(9) | *171(82)* | 764(39) | <0.001*[2,5] <0.001**[2,5] |
| III/IV | 126(60) | 137(54) | 106(54) | 121(61) | 178(62) | 96(48) | 108(38) | 134(64) | 8(9) | 32(15) | 1014(52) | |
| Missing | 32(15) | 11(4) | 11(6) | 4(2) | 7(2) | 4(2) | 9(3) | 7(3) | 72(82) | 5(2) | 157(8) | |
| **Treatment Surgery** n(%) Yes | 57(27) | 107(42) | 84(42) | 65(33) | 81(28) | 113(56) | 168(58) | 65(31) | 36(41) | 199(96) | 975(45) | <0.001*[2,5] <0.001**[2,5] |
| No | 61(29) | 56(22) | 55(28) | 94(47) | 90(32) | 44(22) | 111(39) | 79(37) | 28(32) | 5(2) | 623(29) | |
| Missing | 93(44) | 89(35) | 59(30) | 41(21) | 114(40) | 45(22) | 9(3) | 67(32) | 24(27) | 4(2) | 545(25) | |
| **Treatment Chemo** n(%) Yes | 105(50) | 125(50) | 98(49) | 93(47) | 159(56) | 93(46) | 107(37) | 133(63) | 50(57) | 63(30) | 1026(48) | <0.001*[2,5] <0.001**[2,5] |
| No | 41(19) | 51(20) | 46(23) | 65(33) | 45(16) | 62(31) | 172(60) | 37(18) | 18(20) | 137(66) | 674(32) | |
| Missing | 65(31) | 76(30) | 54(27) | 42(21) | 81(28) | 47(23) | 9(3) | 41(19) | 20(23) | 8(4) | 443(21) | |
| **Treatment Radio** n(%) Yes | 82(39) | 68(27) | 76(38) | 72(36) | 114(40) | 81(40) | 98(34) | 70(33) | 41(47) | 29(14) | 731(34) | <0.001*[2,5] <0.001**[2,5] |
| No | 50(24) | 72(29) | 50(25) | 77(39) | 69(24) | 71(35) | 180(63) | 69(33) | 22(25) | 155(75) | 815(38) | |
| Missing | 79(37) | 112(44) | 72(36) | 51(26) | 102(36) | 50(25) | 10(3) | 72(34) | 25(28) | 24(12) | 597(28) | |
| **Treatment Other** n(%) Yes | 10(5) | 14(6) | 14(7) | 11(6) | 30(11) | 18(9) | 9(3) | 0(0) | 7(8) | 16(8) | 129(6) | <0.001*[2,5] <0.001**[2,5] |

| | Wales (N=211) | England (N=252) | Scotland (N=198) | N Ireland (N=200) | Denmark (N=285) | Manitoba (N=202) | Ontario (N=288) | Sweden (N=211) | Norway (N=88) | Victoria (N=208) | Overall (N=2143) | p-value[6] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No | 48(23) | 63(25) | 45(23) | 69(35) | 255(89) | 3(1) | 261(91) | 0(0) | 2(2) | 138(66) | 884(41) | |
| Missing | 153(72) | 175(69) | 139(70) | 120(60) | 0(0) | 181(90) | 18(6) | 211(100) | 79(90) | 54(26) | 1130(53) | |

[1]Differences between jurisdictions were tested by the Kruskal-Wallis test, [2] Differences between jurisdictions were tested by the Pearson's Chi[2] test, [3]Comorbidity coded as none=no reported, medium=1-2 reported and high=3+ reported, [4] This included cases which could not be mapped as they were classified as per Cancer Registry of Norway into local (stage I), regional (stage II-III) and distant (stage IV) [5]Excluding Victoria, [6]Excluding Norway, *Missing category is excluded, **Missing category is included,
Abbreviations: IQR=inter-quartile range.

*Routes to diagnosis*

Results are detailed in Table 3. Over half (55%) were diagnosed following presentation to the PCP of whom 63% (range: 29% Norway - 82% Wales; data not shown) were urgently referred with a suspicion of cancer, based on the PCP questionnaire.

**Table 3.** Routes to diagnosis of lung cancer patients for each jurisdiction. All figures are n(%) unless otherwise stated.

| | Wales (N=211) | England (N=252) | Scotland (N=198) | N Ireland (N=200) | Denmark (N=285) | Manitoba (N=202) | Ontario (N=288) | Sweden (N=211) | Norway (N=88) | Victoria (N=208) | Total (N=2143) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Symptoms prompting visit to PCP | 109(52) | 150(60) | 128(65) | 131(66) | 170(60) | 101(50) | 91(32) | 65(31) | 35(40) | 106(51) | 1086(51) |
| Symptoms prompting emergency (A&E) department visit[1] | 11(5) | 18(7) | 12(6) | 22(11) | 21(7) | 25(12) | 39(14) | 18(9) | 3(3) | 6(3) | 175(8) |
| Symptoms prompting visit to PCP and emergency (A&E) department[1] | 10(5) | 4(2) | 7(4) | 18(9) | 8(3) | 15(7) | 12(4) | 8(4) | 5(6) | 3(1) | 90(4) |
| Incidental diagnosis in course of investigation/treatment for another problem[2] | 68(32) | 37(15) | 36(18) | 19(10) | 55(19) | 57(28) | 116(40) | 107(51) | 32(36) | 90(43) | 617(29) |
| Unknown routes to diagnosis[3] | 10(5) | 17(7) | 11(6) | 5(3) | 16(6) | 4(2) | 14(5) | 11(5) | 8(9) | 0(0) | 96(5) |
| Other[4] | 3(1) | 25(10) | 3(2) | 4(2) | 14(5) | 0(0) | 16(6) | 2(1) | 5(6) | 3(1) | 75(3) |
| Missing | 0(0) | 1(0.4) | 1(0.5) | 1(0.5) | 1(0.4) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 4(0.2) |

[1] Emergency (A&E) route was ascribed when the patient reported pathway to cancer diagnosis involving going or being taken to the emergency department or the PCP reported that the patient presented to emergency department with or without their involvement [2] this could be by PCP, another doctor or via hospital; [3]includes cases where PCP or patient reported routes to diagnosis as 'Other' or 'Missing' but also reported symptoms or duration of symptoms, or date of first symptom, or waiting time for PCP appointment; [4]includes cases where PCP or patient reported routes to diagnosis as 'Other' and hasn't reported any symptoms or duration of symptoms, or date of first symptom, or waiting time for PCP appointment.

*Symptoms prompting visit to physician*

The median number of patient-reported symptoms were 2 (IQR 1,3). Across jurisdictions, the most common patient-reported symptoms were persistent cough (39%), breathlessness (37%) and fatigue (27%) although there was significant variation in proportion of patients presenting with individual symptoms (Table 4).

The PCPs reported a median of 1 (IQR 1,2) symptom at first presentation, with the most common being persistent cough (39%). Across jurisdictions, the reporting of other symptoms by the PCP was significantly lower compared to patients, especially fatigue (4%) and weight loss (8%). When the analysis was restricted to the cohort where both patient and PCP had completed the survey, this difference persisted. Unlike patients, there was minimal variation in PCP reporting of symptoms, with significant differences limited to 'no symptoms', 'other symptoms not previously listed' and weight loss. Overall 64% of symptoms were labelled as 'cancer specific' by the study PCPs (Table 4).

**Table 4.** Symptoms experienced by patients and presenting symptoms noted by PCP for eligible patients. All figures are n(%)

| | Wales | England | Scotland | N Ireland | Denmark | Manitoba | Ontario | Sweden | Norway | Victoria | Overall | p[1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Symptoms (reported by patient)** | (N=211) | (N=252) | (N=198) | (N=200) | (N=285) | (N=202) | (N=288) | (N=211) | (N=88) | (N=208) | (N=2143) | |
| persistent cough | 113(54) | 123(49) | 97(49) | 83(42) | 97(34) | 71(35) | 125(43) | 84(40) | 10(11) | 39(19) | 842(39) | <0.001 |
| breathlessness | 109(52) | 126(50) | 82(41) | 73(37) | 99(35) | 63(31) | 119(41) | 77(36) | 12(14) | 24(12) | 784(37) | <0.001 |
| fatigue | 75(36) | 79(31) | 64(32) | 61(31) | 38(13) | 55(27) | 92(32) | 60(28) | 17(19) | 42(20) | 583(27) | <0.001 |
| weight loss | 38(18) | 39(15) | 44(22) | 37(19) | 41(14) | 29(14) | 36(13) | 34(16) | 9(10) | 20(10) | 327(15) | 0.147 |
| felt sick /vomiting /nausea/loss of appetite | 42(20) | 33(13) | 31(16) | 24(12) | 33(12) | 22(11) | 45(16) | 28(13) | 3(3) | 20(10) | 281(13) | 0.132 |
| coughing up blood-stained phlegm (sputum) | 35(17) | 32(13) | 24(12) | 31(16) | 21(7) | 16(8) | 27(9) | 25(12) | 5(6) | 23(11) | 239(11) | 0.014 |
| chest or shoulder pain | 23(11) | 9(4) | 18(9) | 24(12) | 10(4) | 28(14) | 43(15) | 25(12) | 4(5) | 22(11) | 206(10) | <0.001 |
| other symptoms not listed above | 51(24) | 80(32) | 59(30) | 54(27) | 63(22) | 40(20) | 30(10) | 75(36) | 26(30) | 42(20) | 520(24) | <0.001 |
| no symptoms | 29(14) | 24(10) | 32(16) | 21(11) | 63(22) | 50(25) | 67(23) | 36(17) | 33(38) | 75(36) | 430(20) | <0.001 |
| missing | 1(0.5) | 16(6) | 6(3) | 17(9) | 31(11) | 9(4) | 4(1) | 4(2) | 12(14) | 1(0.5) | 101(5) | <0.001 |
| **Presenting symptom (reported by PCP)** | (N=85) | (N=133) | (N=115) | (N=0) | (N=151) | (N=86) | (N=61) | (N=0) | (N=17) | (N=81) | (N=729) | |
| persistent cough | 33(39) | 57(43) | 45(39) | n/a | 67(44) | 24(28) | 18(30) | n/a | 7(41) | 33(41) | 284(39) | 0.093 |
| breathlessness | 17(20) | 27(20) | 20(17) | n/a | 27(18) | 11(13) | 11(18) | n/a | 4(24) | 13(16) | 130(18) | 0.803 |
| fatigue | 1(1) | 5(4) | 3(3) | n/a | 9(6) | 2(2) | 2(3) | n/a | 1(6) | 3(4) | 26(4) | 0.539[2] |
| weight loss | 5(6) | 9(7) | 15(13) | n/a | 19(13) | 3(3) | 2(3) | n/a | 0(0) | 5(6) | 58(8) | 0.027 |
| felt sick /vomiting /nausea/loss of appetite | 1(1) | 1(0.8) | 2(2) | n/a | 6(4) | 2(2) | 0(0) | n/a | 0(0) | 0(0) | 12(2) | 0.418[2] |
| coughing up blood-stained phlegm (sputum) | 8(9) | 10(8) | 10(9) | n/a | 7(5) | 2(2) | 3(5) | n/a | 0(0) | 7(9) | 47(6) | 0.305 |
| chest or shoulder pain | 8(9) | 10(8) | 15(13) | n/a | 15(10) | 1(1) | 7(12) | n/a | 1(6) | 4(5) | 61(8) | 0.08 |
| other symptoms not listed above | 24(28) | 44(33) | 33(29) | n/a | 64(42) | 15(17) | 7(12) | n/a | 7(41) | 20(25) | 214(29) | <0.001 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| no symptoms | 5(6) | 6(5) | 6(5) | n/a | 2(1) | 31(36) | 12(20) | n/a | 0(0) | 10(12) | 72(10) | <0.001 |
| missing | 7(8) | 7(5) | 11(10) | n/a | 16(11) | 12(14) | 6(10) | n/a | 2(12) | 10(12) | 71(10) | 0.392 |
| **Cancer-specificity of symptom presented** | | | | | | | | | | | | |
| cancer-specific symptom | 62(73) | 97(73) | 79(69) | n/a | 94(62) | 36(42) | 38(62) | n/a | 10(59) | 48(59) | 464(64) | <0.001 |
| non-specific symptom | 11(13) | 23(17) | 19(17) | n/a | 39(26) | 7(8) | 5(8) | n/a | 5(29) | 13(16) | 122(17) | |
| no symptoms /missing | 12(14) | 13(10) | 17(15) | n/a | 18(12) | 43(50) | 18(30) | n/a | 2(12) | 20(25) | 143(19) | |

[1] Differences between jurisdictions (excluding Victoria and Norway) were tested by the Pearson's Chi[2] test, if nothing else stated.
[2] Differences between jurisdictions (excluding Victoria and Norway) were tested by the Fisher's exact test.

*Time intervals*

The observed time intervals are shown in Appendix C2 and are summarised in Figure 2. Based on overall trends, jurisdictions could be grouped into those with reduced, longer and similar intervals to Wales (Table 5). It was not possible to interpret variations observed in Norway (small sample size) and Victoria (surgical cohort). In the remaining jurisdictions, there was no difference in the median adjusted patient interval compared to Wales. Denmark had shorter median adjusted primary care interval (-11 days); Sweden had shorter (-20) and Manitoba longer (+40) diagnostic intervals compared to Wales. Denmark (-13), Manitoba (-11), England (-9) and Northern Ireland (-4) had shorter treatment intervals. The median adjusted total interval was shorter only in Denmark (Table 5, Figure 2). The differences were greater for the 90th percentile. The total interval in patients who waited longest (90th percentile) was significantly shorter in two jurisdictions (Denmark -142, England -28 days) compared to Wales.

**Table 5.** Differences in adjusted intervals (days) between Wales and the other nine jurisdictions for lung cancer patients

| Intervals | percentiles | Wales | Denmark | Sweden | England | N Ireland | Scotland | Manitoba | Ontario | Norway | Victoria |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Reference in days | Overall trend - shorter intervals | | | Similar with some intervals longer, some shorter | | Overall trend - longer intervals | | Difficult to interpret (see text for reasons) | |
| Ranking by 5-year survival rates for lung cancers diagnosed in 1999-2007 [5] | | 10 | 6 | 1 | 9 | 7 | 8 | 3 | 2 | 5 | 4 |
| Patient Interval | Number of patients | 181 | 233 | 172 | 213 | 179 | 169 | 133 | 205 | 55 | 141 |
| | 50th percentile (95% CI) | 21 | -6 (-13,0) | -1 (-9,8) | -3 (-10,5) | -3 (-13,6) | -3 (-10,4) | 1 (-8,10) | 1 (-11,14) | 0 (-8,8) | **-9** (-16,-2) |
| | 75th percentile (95% CI) | 61 | -13 (-38,13) | -2 (-24,21) | -2 (-42,37 ) | -8 (-55,39) | 1 (-25,27) | 3 (-23,30) | -7 (-54,39) | -9 (-60,42) | -4 (-46,38) |
| | 90th percentile (95% CI) | 216 | **-34** (-55,-13) | -1 (-25,23) | -15 (-42,12) | 24 (-21,70) | **43** (7,79) | **-35** (-59,-10) | **-34** (-66,-2) | **59** (21,96) | **-35** (-49,-21) |
| Primary Care interval | Number of patients | 110 | 159 | N/A | 147 | 124 | 119 | 80 | 75 | 19 | 89 |
| | 50th percentile (95% CI) | 20 | **-11** (-18,-3) | | -7 (-17,3) | -5 (-15,4) | -3 (-14,8) | 7 (-8,21) | 5 (-9,19) | **-11** (-18,-4) | -8 (-17,1) |
| | 75th percentile (95% CI) | 43 | **-29** (-47,-12) | N/A | -17 (-42,8) | 1 (-45,48) | -11 (-36,14) | 19 (-47,85) | 20 (-72,112) | -10 (-57,37) | -12 (-70,46) |
| | 90th percentile (95% CI) | 91 | -30 (-66,7) | | -39 (-85,6) | 17 (-55,90) | -20 (-67,25) | 13 (-38,65) | 102 (-56,258) | -22 (-109,66) | -19 (-89,51) |
| Diagnostic interval | Number of patients | 176 | 229 | 165 | 212 | 170 | 173 | 138 | 212 | 52 | 160 |
| | 50th percentile (95% CI) | 45 | -12 (-25,1) | **-20** (-35,-5) | 9 (-3,21) | 17 (-5,39) | -4 (-16,8) | **40** (14,66) | 10 (-6,26) | 4 (-16,24) | 7 (-13,27) |
| | 75th percentile (95% CI) | 108 | **-45** (-52,-39) | **-22** (-30,-15) | -7 (-20,7) | **12** (2,22) | -15 (-32,1) | **35** (22,48) | 5 (-9,19) | -4 (-15,8) | -2 (-8,4) |
| | 90th percentile (95% CI) | 162 | -27 (-153,99) | -34 (-206,138) | -14 (-100,72) | 112 (-165,389) | 31 (-81,143) | **112** (32,192) | 106 (-122,335) | 0 (-93,93) | **62** (10,114) |
| Treatment interval | Number of patients | 192 | 279 | 190 | 238 | 200 | 187 | 182 | 263 | 87 | 199 |
| | 50th percentile (95% CI) | 43 | **-13** (-15,-11) | -2 (-8,3) | **-9** (-12,-5) | **-4** (-7,-2) | 0 (-4,4) | **-11** (-17,-5) | 3 (-4,10) | **-8** (-11,-6) | **-29** (-32,-27) |
| | 75th percentile (95% CI) | 64 | **-32** (-36,-28) | -2 (-8,4) | **-18** (-23,-13) | **-13** (-18,-7) | 1 (-7,9) | -5 (-16,6) | 6 (-2,14) | **-13** (-19,-8) | **-33** (-41,-25) |
| | 90th percentile (95% CI) | 89 | **-45** (-50,-40) | **-10** (-17,-4) | **-28** (-36,-20) | **-16** (-23,-9) | -6 (-14,1) | 4 (-5,13) | 4 (-4,13) | **-22** (-30,-14) | **-39** (-45,-32) |
| Total | Number of patients | 147 | 192 | 147 | 176 | 153 | 143 | 117 | 178 | 52 | 113 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| interval | 50th percentile (95% CI) | 116 | **-49** (-95,-3) | -8 (-64,47) | -7 (-52,38) | -16 (-41,10) | -2 (-70,66) | 11 (-41,63) | 9 (-78,97) | **-34** (-56,-12) | -32 (-64,2) |
| | 75th percentile (95% CI) | 204 | -91 (-270,87) | -17 (-40,7) | -29 (-175,118) | 5 (-191,201) | 33 (-144,211) | 13 (-77,103) | -7 (-331,317) | -39 (-107,29) | -23 (-61,14) |
| | 90th percentile (95% CI) | 365 | **-142** (-150,-134) | -18 (-59,23) | **-28** (-37,-18) | 0 (-4,5) | 15 (-26,55) | 15 (-26,55) | 0 (-78,79) | **-84** (-119,-49) | 0 (-3,3) |

| **Interval relative to Wales** | **Trends** | **Significant** |
|---|---|---|
| Reduction | | |
| Increase | | |

The majority of patients were diagnosed between 2013-14. The differences were calculated for the 50th, 75th and 90th percentiles by setting age to its mean value and gender and comorbidity to their modes (i.e. male gender and medium comorbidity). It is not possible to interpret differences observed for Norway (due to the small sample size) and Victoria (the cohort was limited to those who had undergone surgery).

FIGURE 2

*Sensitivity and validity analyses*

The estimates of routes to diagnosis, time intervals, and regression analysis trends were not significantly altered by changing the cut-off to 6 months or using only patient data (results not shown).

Appendix C3 details, which sources were used based on the standardization rules, to define dates and also how often a day in the date was imputed. With regards to the dates of first presentation to healthcare (CCC=0.91), diagnosis (CCC ≥ 0.93) and treatment (CCC=0.94), there was adequate agreement between all data sources where the data on these dates was collected. Agreement between patient versus PCP for dates of first presentation to healthcare (CCC=0.91) and diagnosis (CCC=0.93) was also adequate as was agreement between patient versus CTS for dates of diagnosis (CCC=0.94) and treatment (CCC=0.94).

Omitting time intervals which were negative or over 365 days (Appendix C4) led to change in direction of difference which was non-significant in long intervals (75th or 90th percentile) between Wales and jurisdictions in four cases: Norway and Victoria (patient interval), N Ireland (diagnostic interval), England (total interval). All other results were similar to the main results.

## Discussion

*Main findings*

This is the first international study we are aware of comparing lung cancer routes and time intervals. With the exception of Denmark, in all other jurisdictions, the median total interval

from symptom onset to treatment, for respondents diagnosed in 2012-15 was similar to that of Wales, the reference. However, there were jurisdiction specific differences in patient, diagnostic and treatment intervals, especially for the 10% of patients who waited the longest. Based on overall trends, jurisdictions could be grouped into those with trends of reduced, longer and similar intervals to Wales.

Across jurisdictions, all symptoms other than persistent cough were less frequently reported by the PCP when compared to patients. This was especially true for fatigue and weight loss. One in four patients reported incidental diagnosis and one in ten were diagnosed following a visit to the emergency (A&E) department.

*Strengths and weaknesses*

Our study helps address the shortcomings of current international comparisons across multiple national studies with significant variation in methodology including differences in definition of intervals. Strengths of our study include 1) use of the same methodology across countries 2) use of cancer registries to identify consecutive newly diagnosed patients; 3) use of standardised questionnaires; 4) inclusion of PCP and CTS questionnaires enriched by registry data; 5) minimal data interpretation by the local teams with all data cleaning performed in a standardised manner centrally; and 6) triangulation with comprehensive data rules to ensure validity, consistency and preserve statistical precision.[21] Recall bias was minimised by the triangulation of different data sources and by patients completing the questionnaire within a limited time window (median 5 months) after the cancer diagnosis.

A key limitation, as with all questionnaire-based studies was both selection and non-response bias which varied across jurisdictions and has implications for interpretation and generalisation of findings. In comparing intervals, we adjusted for age, sex and comorbidity but were unable to adjust for ethnicity and education due to different classification systems. Recall bias was minimised by the triangulation of different data sources and by patients completing the questionnaire within a limited time window (median 5 months) after the cancer diagnosis. Recruitment of patients up to 9 rather than 6 months after diagnosis might have magnified the selection bias due to high mortality.[34] However, sensitivity analysis suggests that this did not impact on the results. Categorising presenting symptoms into indicative or not was done pragmatically as existing guidelines for lung cancer investigation vary across ICBP jurisdictions.[35] In Norway and Victoria, a small sample size and restriction of eligibility to only surgical patients, respectively, made comparison difficult. Nonetheless, significant differences in these two jurisdictions compared to Wales were largely limited to the treatment interval alone.

There was variation in stage distribution across jurisdictions. While this may be partly related to the varying response rate, true differences in lung cancer stage have been noted on analysis of registry data of patients diagnosed between 2004-2007.[6] The high lung cancer mortality and self-selection are likely to have contributed to an over-representation of early stage disease and tumours treated with surgical resection. This suggests that true variation may well be higher than that reported in this cohort of 'healthier early stage' patients.

*Comparison to other studies*

The most common patient-reported symptoms, in keeping with the literature, were persistent cough, breathlessness, fatigue and weight loss, with one in five reporting 'no symptoms'.[18] Only a minority (11%) of our respondents reported coughing blood or bloody sputum/spit, which is the only consistent predictor of lung cancer.[36] While haemoptysis was reported in a prospective survey (England 2011-12) by 22% of lung cancer patients identified through respiratory clinics, it was a presenting symptom in only 5% of cases.[11]

The median number of symptoms reported by patients was more than that reported by the PCP in all jurisdictions. This was especially so for fatigue and weight loss. A number of factors could have contributed to this - patients not listing all symptoms at presentation, patients having a different understanding/recall of their symptoms post diagnosis, PCPs only recording key symptoms such as cough. Further research on under reporting of systemic symptoms such as fatigue and weight loss is warranted.

As lung cancer mortality is higher in patients attending emergency (A&E) departments, the rates are often compared in an attempt to understand international survival differences.[37] The rate of respondents who attended A&E varied two-fold across jurisdictions from 9-10% in England, Scotland and Denmark to 18-20% in Northern Ireland, Ontario and Manitoba. While rates for Scotland (10%) were similar to that reported in a prospective Scottish audit (11.5%), as were rates for Denmark (7% vs 6.3% when PCP not involved), rates for England (9%) were lower than those reported in population based audits (25%) reflecting non-response bias.[14,15] In Victoria (4%) restriction of the cohort to surgical patients is likely to have accounted for the very low rates.

Our reported median patient, primary care and diagnostic intervals are in keeping with those previously reported from the participating jurisdictions (Table 6). Minor variations in interval estimates are likely due to differences in data source, sample size and cohort characteristics.[38] Longer intervals were reported from earlier cancer cohorts - median

primary care interval for England of 52 days in 1998-2000 (our median 11),[13] median total interval for Denmark of 108 days in 2004-5 (our median 67) and Norway of 118 in 2002-5 (our median 79).[17-19,24]

**Table 6.** Summary of literature on intervals in lung cancer patients diagnosed since 2000 in the ICBP Module 4 countries

| Study No | Ref | Study Period | Jurisdiction | Design | Patients | No. of lung cancer patients | Interval[1] (days) | | | | Total interval |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Patient | Primary care | Diagnostic | Treatment | |
| 1 | Walter FM et al (2015) | 2011-2 | England, UK | Prospective patient questionnaire survey - multi hospital cohort. Dates of diagnosis based on medical note review. | All attending urgent and routine respiratory clinics across the five hospitals in England aged over 40 years with symptoms suspicious of lung cancer. | 153 | Interval from first symptom to diagnosis Median 91 (IQR 49-184) | | | | |
| 2 | Lyratzopoulos G et al (2015) | 2009-10 | England, UK | Prospective national audit of cancer diagnosis using primary practice patient records and continuous sampling during audit period | All patients aged ≥15 years who had first presented to a primary care practitioner and were subsequently diagnosed with one of 28 cancers | 1128 | Median 11 (IQR 0-32) | Median 3 (IQR 14-39) | | | |
| 3 | Neal R et al (2014) | 2007–8 | UK | Retrospective analysis of electonic health record data from General Practice Research Database - population cohort | All newly diagnosed with one of 15 cancers | 2851 | | | Median 112 (IQR 45-251) | | |
| 4 | Barrett J et al (2008) | 1998-2002 | Exeter, England, UK | Retrospective case-control review of PCP records - population cohort | All with lung cancer aged ≥ 40 years, identified from the hospital cancer registry and computerised searches of all primary care practices | 247 | | Median 52 (IQR 7–243) | | | |
| | | | | | | | Interval from first symptom to diagnosis - Median 121 (IQR 53,261) | | | | |
| 5 | Baughan P et al (2009) | 2005-6, 2007-8 | Scotland, UK | Retrospective audit involving PCP review of medical records of all newly diagnosed cancer patients they had seen - population cohort | All newly diagnosed with lung cancer | 981 | Median 9.5 (IQR 31) | | Median 11 (IQR 28) | | |
| 6 | Guldbrandt LM et al (2015) | 2010 | Denmark | Retrospective PCP questionnaires survery of national registry-based population cohort | All consecutive newly diagnosed lung cancer patients | 429-442 depending on interval | | Median 7 (IQR, 0-30) | Median 29 (IQR, 12-69) | | |
| 7 | Tørring ML et al (2013) | 2004 - 5 | Aarhus, Denmark | Prospective, population-based study using electronic health records and PCP survey of identified patients | All newly diagnosed with lung cancer after attending primary care | 262 | | | Median 112 (IQR 45-251) | | |
| 8 | Hansen RP et al (2011) | 2004-5 | Aarhus, Denmark | Retrospective PCP survey | Cancer patients newly diagnosed during a 1-year period identified using administrative registry data | 128-251 (depending on interval) | Median 28 (IQR 7-56) | Median 0 (IQR 0-9) | | Median 51 (IQR 27-76) | Median 108 (IQR 82-167) |
| 9 | Bjerager M et al (2006) | 2003 | Aarhus, Denmark | Retrospective PCP survey using structured telephone interviews enriched with administrative registry data - population-based cohort | All lung cancer patients identified through histological and cytological tests from county-based registers | 84 | | Median 32.5 (IQR 12–68) | | | |
| 10 | Rolke HB et al (2006) | 2002-5 | Norway (South) | Retrospective questionnaire-based patient survey - hospital cohort | All newly diagnosed with lung cancer | 273 -376 (depending on interval) | Median 19 (2–77) | | | | Median 118 (IQR 68–220) |
| 11 | Stokstad T et al (2017) | 2011-13 | Norway | Retrospective medical record audit -single hospital cohort | All cases that started diagnostic work-up and were diagnosed with lung cancer at St. Olavs Hospital, Trondheim | 449 | | | | 42 days (range: 2–296) | |
| 12 | Largey G et al (2016) | 2013 | Victoria, Australia | Retrospective medical record audit -three hospital cohort | Admitted with a new diagnosis of lung cancer over a three month period in three hospitals | 78 | | | | Mean 30.4 (SD 45.3) | |
| 13 | Evans SM et al (2016) | 2011-4 | Victoria, Australia | Retrospective medical record audit - multi hospital cohort | All lung cancer patients newly diagnosed in six public and two private hospitals | 1417 | | | Median 15 (IQR, 5–36) | Median 30 (IQR, 6–84) | |
| 14 | Emery JD et al (2017) | 2012 -4 | Western rural Australia | Prospective cluster randomised trial of symptom awareness | Lung cancer patients newly diagnosed in the control arm of the trial | 167 | Interval from first symptom to diagnosis Median 34.5 (IQR 7 103.5) | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 15 | Burneister BH et al (2010) | 2000-4 | Queensland Australia | Retrospective analysis of radiation therapy waiting times | All lung cancer patients who received radiation therapy as initial treatment at a public hospital. | 1535 | | | | | Median 33[2] |
| 16 | Ellis PM and Vandermeer R (2011) | 2010 | Ontario, Canada | Retrospective patient survey using structured telephone interviews - single centre cohort. Appointment dates and diagnostic tests verified through family doctor or patient chart review. | All lung cancer patients referred to a regional cancer centre | 52 | | Median 21 | Median 27 (IQR 0-38) | | Median 138 (IQR 79-175) |
| 17 | Lo DS et al (2007) | 2005-7 | Ontario, Canada | Retrospective medical record audit - multi hospital cohort | All with lung cancer seen on a newly implemented Time to Treat Program | 144 | | | Median interval from suspicion of lung cancer to diagnosis 37 | | |

[1] Intervals as defined in Figure 1; [2] Limited to patients receiving radiation treatment

Across all jurisdictions, there was no significant difference in primary care intervals for the 10% of patients with longest interval. It is likely that these patients had vague or non-specific symptoms and signs. Referral guidelines for suspected lung cancer do not always favour patients with early symptoms and often prioritise those with more advanced disease.[39] Access to better diagnostic tools such as low-dose CT chest in the primary care setting may favour this group of patients.[40] It would be useful in future projects to explore whether such access may have contributed to the improved 1-year lung cancer survival rates reported from Australia and Canada.[6]

Diagnostic intervals were significantly longer for Manitoba compared to other jurisdictions and twice that reported in an ongoing local PCP audit (personal communication). While one might suspect overestimation due to differences in the source of date of first presentation, between our study (in almost half, it was derived from patients) and local audit, this is less likely as the concordance coefficient between PCP and patient derived data at Manitoba was 0.94.

Observed median treatment intervals were below 6 weeks for nearly all jurisdictions. This was the only interval where there were significant differences between jurisdictions with Denmark, England, Norway and Northern Ireland all having shorter adjusted treatment intervals across all percentiles, with larger differences for the 75$^{th}$ and 90$^{th}$ percentile. These improvements may reflect implementation of waiting time targets in Denmark (35-38 days from first consultation depending on treatment modality) and the UK (31 days from decision to treat).[41,42] The shorter treatment intervals in Norway are in keeping with long-standing provision of standardized cancer care pathways and effective coordination between primary care and treatment centers. While a systematic review did not find evidence to support an association between intervals and lung cancer outcomes, increasing mortality with longer diagnostic intervals was noted in a more recent, high-quality study.[16] In 2000, O'Rourke reported median intervals of 94 days (35-187) between the first hospital visit and starting treatment resulting in 21% of potentially curable patients becoming incurable.[43] Others have found metabolic evidence on PET/CT of pre-treatment disease progression in 21% and TNM upstaging in 18% of small-cell lung cancer patients after a relatively short median inter-scan interval of 43 days.[44] Long intervals can also result in deterioration in performance status. More recently, there is concern that the need for genotyping may result in further increase in time to treatment.

The shorter total interval in Denmark likely reflects the significant reductions in cancer waiting times following a collaborative effort to set-up and implement a national centralised quality

management system, the Danish Cancer Patient Pathways (CPPs). The latter includes PCP access to fast-track diagnostic work-up.[45]. The findings are in keeping with higher relative survival and lower mortality in Denmark among symptomatic cancer patients diagnosed through primary care after the implementation of CPPs and with the accelerated increase in 5-year survival among Danish lung cancer patients diagnosed in 2010-2014 when compared to patients from earlier time periods.[46] While there is some inherent lead-time bias, the findings highlight the importance and feasibility of a timely diagnosis of lung cancer.

*Conclusions*

The study provides for the first time, robust data, collected through consistent methods in all jurisdictions, allowing for detailed comparisons of key diagnostic intervals in lung cancer and routes to diagnosis. While all jurisdictions except Denmark, had similar median adjusted total intervals, there were jurisdiction-specific significant differences in patient, diagnostic and treatment intervals, especially for the 10% of patients who waited the longest. The proportion of patients diagnosed following presentation to the PCP ranged from 35-75%. These data could help individual jurisdictions to better target their efforts to reduce time to treatment and ultimately improve patient experience and outcomes in lung cancer.'

Intervals and pathways are ultimately of interest as they relate to prognosis. A further analysis which includes all four cancers (lung, ovary, colon and breast) surveyed in ICBP4 module and explores the impact of these intervals on stage and 1-year survival is underway.

**List of abbreviations**

ICBP M4 – International Cancer Benchmarking Partnership Module 4

PCP – Primary Care Physician

CTS – Cancer Treatment Specialist

CPP – Danish Cancer Patient Pathways

**Figure headings**

Figure 1: Time intervals from onset of symptoms to start of treatment based on the Aarhus Statement

Figure 2: Differences in 50th, 75th and 90th centiles of the intervals (days) between Wales as the reference and the other nine jurisdictions. The data are adjusted for differences in age, gender and comorbidity. The bars in black show significant differences in intervals.

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**Author's contribution**

UM, DW, PV, AZF, HJ planned the study design, data collection, carried out the analyses and wrote the draft manuscript. UM, PV, DW, HJ, AB, AKK, RJB, DHB, JK, VC, ATG, EG, EH, ML, RJW, YL, MM, DT, RDN, VW, IR and SH were responsible for local data collection (alongside the Working Group), management and interpretation, and have participated in writing and have approving the final manuscript version. JB, OB and OTB provided advice on the interpretation of results in their respective jurisdictions and comments or substantial edits on the manuscript, approving the final version.

**Competing Interests**

None

**Data Availability statement**

No additional data avaliable

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**Availability of data and material**

The data that support the findings of this study are available from the named authors from each ICBP jurisdiction, but restrictions apply to the availability of these data and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the ICBP Programme Board. Please contact the ICBP Programme Management team, based at Cancer Research UK, with any queries (icbp@cancer.org.uk).

**Ethics approval and consent to participate**

For each local data collection, there were specific procedures and approvals which included anonymised data transfer to University College London and Aarhus University. Approvals were received from the following institutions: Cancer Council Victoria Human Research Ethics Committee [HREC 1125]; Health Research Ethics Board, University of Manitoba [HS15227 (H2012:105)]; Research Resource Ethics Committee, CancerCare Manitoba [RRIC#28-2012]; University of Toronto Research Ethics Board [27881]; The Danish Data Protection Agency [2013-41-2030]; Swedish Ethics Review Board, Uppsala [2013/306]; Norway Regional

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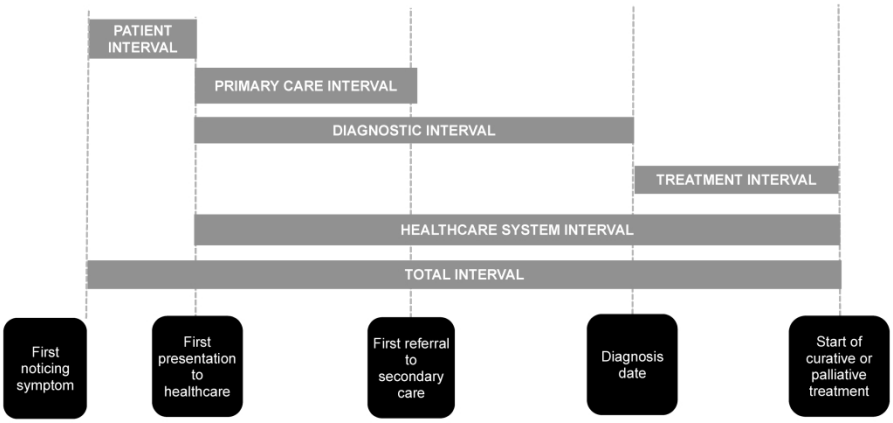
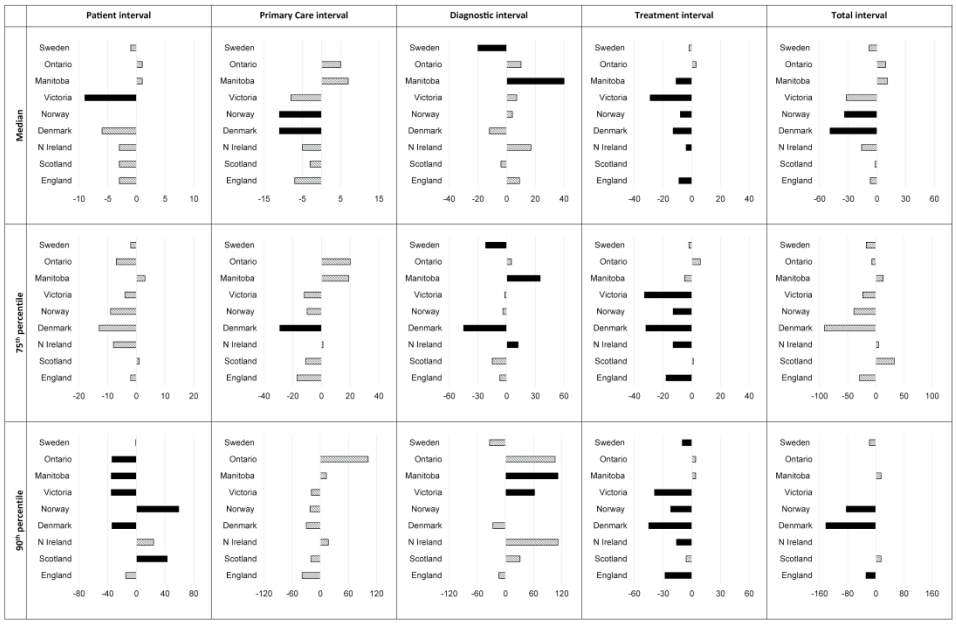



Time intervals from onset of symptoms to start of treatment based on the Aarhus Statement




Differences in 50th, 75th and 90th centiles of the intervals (days) between Wales as the reference and the other nine jurisdictions. The data are adjusted for differences in age, gender and comorbidity. The bars in black show significant differences in intervals.

420x297mm (300 x 300 DPI)

# Supplementary Web Appendix

## Contents

## Appendix A: Lung cancer questionnaires

A1: Patient questionnaire

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# International Cancer Benchmarking Partnership Module 4

## Patient questionnaire

## Lung Cancer

Thank you very much for taking the time to fill in this questionnaire – it should take about 20 minutes to complete. We are sending the questionnaire to a large sample of people who we understand have had a diagnosis of lung cancer. If this has been sent to you in error and you do not have cancer, please do not continue and return the documents in the prepaid envelope.



Our aim is to gain a better understanding of the process by which people have their cancer diagnosed. We would also like to find out more about the symptoms they experience (if any), and the pathway they follow from start of symptoms to treatment of their cancer. This will help in identifying ways in which cancers can be diagnosed quickly and effectively. Thank you once again for your time.

**This information is confidential and will not be passed to anyone involved in your treatment.**

Name: _____

Date of Birth: _____

Address: _____

_____

_____

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## Consent form

Please read the consent form and sign your name and date **BELOW**.

If you require any clarification, please do not hesitate to ring the study team members. Their contact details are found on the information sheet.

**Please be reassured that your responses are completely confidential and will not be passed to anyone involved in your treatment. For the purposes of the study it is important that you agree to consent to all the statements listed below.**

- I confirm that I have read the attached information sheet and I understand why the research is being done.
- I am willing for the team to request information from my GP and hospital doctors which is relevant to the audit as described in the information sheet.
- I give permission for my details (name, address) to be given to the cancer registry (NHS Information Centre for Health and Social Care) for follow up.
- I agree for the information I have provided and any other relevant information from my medical records to be stored as described in the information sheet under the custodianship of University College London.
- I consent to sharing of coded data which contains no personal identifiers between researchers, some of whom are located outside the European Union.
- I consent for use of my data if I become mentally incapacitated during the course of the project.

**I agree to all the statements listed and consent to participate in the study.**

Name (Please print) _____

Signature: _____ Date: _____

If we have any questions, may we phone you for clarification?
(Please tick) ☐ **Yes** ☐ **No**

If **Yes**, please provide your telephone number: _____

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**1. Please can you confirm the details of your GP/GP practice (name, practice address – as best as you can remember): We appreciate that you may have more than one GP involved in your care – in which case, we are interested in the GP you would say provides the majority of your care, particularly relating to the cancer you've had diagnosed.**

Name of doctor

Name of practice

Address

Postcode

Town

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**2. Which of the following best describes the events which led to your diagnosis of cancer?** (please tick only **ONE** answer)

| | ✓ |
|---|---|
| I had symptoms/I noticed a bodily change and went to see a doctor (e.g. GP) | |
| I had symptoms/I noticed a bodily change and went/was taken to Accident and Emergency (A&E) | |
| I had seen a doctor/GP with symptoms, but went/was taken to Accident and Emergency (A&E) when things worsened | |
| I was being investigated by my doctor(s) for another problem during which time the cancer was discovered | |
| Other (please describe): | |

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**3. The following health concerns or symptoms are commonly experienced with lung cancer.**

| |
|---|
| Cough |
| Breathlessness |
| Being short of breath |
| Chest pain / Pain on breathing |
| Coughing up blood |
| Bloody sputum/blood in spit |
| Unexplained weight loss |
| Loss of appetite |
| Fatigue |



**Please write down ALL health concern(s) or symptom(s) you may have had before contacting a doctor or taking part in screening. It does not matter if they are not included in the list above:**

| Please write your health concern(s) or symptom(s) in the boxes below: |
|---|
| 1) |
| 2) |
| 3) |
| 4) |
| 5) |
| 6) |

| | |
|---|---|
| This is not applicable to me (e.g. I did not have any symptoms), please tick | ✓ |

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**4. Please write down your best estimate of the date you noticed the first of these health concern(s) or symptom(s).** If you cannot remember the exact date, you can fill in the month and the year.

Day (optional), month, year

| D | D | M | M | Y | Y | Y | Y |
|---|---|---|---|---|---|---|---|
| | | | | | | | |

| | ✓ |
|---|---|
| This is not applicable to me (e.g. I had no symptoms), please tick | |

**5. Approximately how long did you have health concern(s) or symptom(s) before contacting a doctor? (Please think of the first visit to the doctor, not re-visits after that).** Please tick only **ONE** answer.

| | ✓ |
|---|---|
| Less than 1 week | |
| 1-2 weeks | |
| 3-4 weeks | |
| 5-7 weeks | |
| 2-5 months | |
| 6-12 months | |
| More than 12 months | |

| | ✓ |
|---|---|
| This is not applicable to me (e.g. I had no symptoms), please tick | |

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**6a. Once you contacted a practice about your health concern(s) or symptom(s), how long did it take to get an appointment with a doctor? (Please think of the first visit to the doctor, to discuss your health concern(s) or symptom(s)).**
Please tick only **ONE** answer.

| | ✓ |
|---|---|
| Same day/next day | |
| Within 1 week | |
| 1-2 weeks | |
| 3-4 weeks | |
| Longer | |
| If there was no waiting time (e.g. you went/were taken to A&E), please tick this box | |
| This is not applicable to me (e.g. I had no symptoms), please tick | |



**6b. What was the date you first saw your doctor about your health concern(s) or symptom(s)?** If you cannot remember the exact date, you can fill in the month and the year.

Day (optional), month, year

| D | D | M | M | Y | Y | Y | Y |
|---|---|---|---|---|---|---|---|

| | ✓ |
|---|---|
| This is not applicable to me (e.g. I had no symptoms), please tick | |

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**7. How many times did you visit the following for the investigation of your symptoms before your cancer was diagnosed?**

| | Please write down the number of visits |
|---|---|
| GP | |
| Hospital | |
| Consultant/specialist outside of a hospital | |

✓

| | |
|---|---|
| This is not applicable to me (e.g. I had no symptoms), please tick | |

**8a. After your doctor referred you to a specialist, how long did it take you to get an appointment?** Please tick only **ONE** answer.

✓

| | |
|---|---|
| Less than 1 week | |
| 1-2 weeks | |
| 3-4 weeks | |
| 5-7 weeks | |
| 2-5 months | |
| 6-12 months | |
| More than 12 months | |

✓

| | |
|---|---|
| This is not applicable to me (e.g. my doctor did not refer me), please tick | |

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**8b. What was the date of your first appointment with a doctor, involved in investigating and/or treating your cancer, to whom you were referred?**
If you cannot remember the exact date, you can fill in the month and the year.

Day (optional), month, year

| D | D | M | M | Y | Y | Y | Y |
|---|---|---|---|---|---|---|---|

| This is not applicable to me (e.g. my doctor did not refer me), please tick | ✓ |
|---|---|

**9. What was the date you were told you had cancer?** If you cannot remember the exact date, you can fill in the month and the year.

Day (optional), month, year

| D | D | M | M | Y | Y | Y | Y |
|---|---|---|---|---|---|---|---|

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**10. Have you had any of the following treatments for your cancer yet? If so, please can you estimate the date this treatment started?** Please tick **ALL** that apply. If you cannot remember the exact date, you can fill in the month and the year.

| | Type of treatment | | Date of treatment (give first date if you had more than one) |
|---|---|---|---|
| a. | Surgery | ☐ Yes ☐ No | Day (optional), month, year D D M M Y Y Y Y |
| b. | Chemotherapy | ☐ Yes ☐ No | Day (optional), month, year D D M M Y Y Y Y |
| c. | Radiotherapy | ☐ Yes ☐ No | Day (optional), month, year D D M M Y Y Y Y |
| d. | Other Please specify: | ☐ Yes ☐ No | Day (optional), month, year D D M M Y Y Y Y |
| e. | Treatment not started yet | ☐ Yes | |

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**11. Who is the consultant doctor who has taken responsibility for diagnosing and or/treating your cancer?**

| |
|---|
| Name of consultant: |
| Hospital name: |
| Hospital department: |

**Please can you answer some more general questions about your health?**
It will help us in interpreting your responses to this questionnaire to know about your general health and other health problems you may have had in the past.

**12. Looking back to the 2 years before you were diagnosed with cancer, would you say your general health was** (Please tick only **ONE** answer.)**:**



| | ✓ |
|---|---|
| Very good | |
| Good | |
| Fair | |
| Poor | |
| Very poor | |

**13. Have you been treated before for any of the conditions below?**
Please tick 'yes' or 'no' for each condition:

| | | |
|---|---|---|
| Heart disease | ☐ **Yes** | ☐ **No** |
| Stroke | ☐ **Yes** | ☐ **No** |
| Lung disease (excluding lung cancer) | ☐ **Yes** | ☐ **No** |
| Diabetes | ☐ **Yes** | ☐ **No** |

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**Finally, a little more information about you.** The information you provide below will help us to analyse the results of the survey in more detail.

**14. Which of these best describes your ethnic group? (please tick one box, as appropriate).** If you are descended from more than one ethnic or racial group, please tick the group you consider you belong to, or tick 'any other ethnic group'.

| | ✓ | | ✓ | | ✓ | | ✓ |
|---|---|---|---|---|---|---|---|
| White | | Chinese | | Black - Caribbean | | Black - African | |
| Black - other | | Indian | | Pakistani | | Bangladeshi | |
| Any other ethnic group, please specify: | | | | | | | |



**15. What is the main language spoken in your home?** Please tick

| | ✓ |
|---|---|
| English | |
| Other, please specify: | |

**16. What is the highest level of education you have achieved?**
Please tick only **ONE** answer.

| | ✓ |
|---|---|
| Finished school at or before the age of fifteen | |
| Completed GCSEs, O-levels or equivalent | |
| Completed A Levels or equivalent | |
| Completed further education but not a degree | |
| Completed a Bachelor's degree / Masters degree / PhD | |
| Other, please specify: | |

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**17. Have you ever smoked cigarettes, including hand-rolled ones, pipes or cigars?**

☐ Yes ☐ No

**18. Are you a current smoker, smoking either cigarettes, including hand-rolled ones, pipes or cigars?**

☐ Yes ☐ No

**19. If you are a current smoker or have smoked in the past, how many cigarettes, including hand-rolled ones, pipes or cigars on average do you smoke/have you smoked per day?**

| Number per day: | |
|---|---|

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## 20. Further comments

**Please add anything else that you would like to tell us about your cancer diagnosis or treatment.**



**Thank you very much for taking the time to complete this questionnaire.**

A2: Primary care physician (PCP) questionnaire

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# International Cancer Benchmarking Partnership Module 4

## Primary Care Audit

## Lung Cancer

Thank you very much for agreeing to fill in this questionnaire. As part of an international study examining differences in cancer survival, we are sending the questionnaire to health care providers of a sample of consented patients with cancer.

Our aim is to gain a better understanding of the process by which people have their cancer diagnosed – the symptoms they experience, and the pathway they follow from onset of symptoms to treatment of their cancer. This will help in identifying ways in which cancers can be diagnosed and treated quickly and effectively. Thank you once again for your time.



**Please can you refer to your patient's notes in completing the questionnaire as this will help in obtaining accurate data on time points.**

If you would prefer to return this questionnaire without the patient details, please tear off along the dotted line

ID-number: Jurisdiction-ID + Patient-ID:

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**Patient information**

ID-number: Jurisdiction-ID + Patient-ID:

Full name:

Address:

Postcode:

Date of birth: D D M M Y Y Y Y

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## 1. Duration of symptoms

Please estimate how long your patient had symptom(s), attributable to lung cancer, before attending your practice (or other health service).

We appreciate that identifying a 'date of first symptom' is not always straightforward – particularly when there are multiple and/or chronic symptoms. Nevertheless, we hope you can provide a 'best estimate'.

| **Estimate of symptom duration** (please tick **one**): | ✓ | **What were the symptoms?** Please describe: |
|---|---|---|
| Less than 1 week | | |
| 1 to 4 weeks | | |
| 5 to 7 weeks | | |
| 2-5 months | | |
| 6-12 months | | |
| More than 12 months | | |
| Not possible to estimate | | |
| No symptoms (e.g. screen detected cancers) | | |

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## 2. Pathway of presentation

### 2.1 Through what route did the patient first present? Please tick **ONE**:

| | ✓ | |
|---|---|---|
| Your patient first presented to primary care (either in-hours or out-of-hours) | | Please can you provide your best approximation of the date of this **primary care** visit<br>D D M M Y Y Y Y |
| Your patient presented straight to A&E (with or without your involvement) | | |
| Your patient first presented to primary care, but then at a later date presented to A&E as an emergency (with or without your involvement) | | Please can you provide your best approximation of the date of this **primary care** visit<br>D D M M Y Y Y Y |
| Other – please describe: | | |

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**3. Date you ordered any tests/investigations in response to symptom(s).**

We are interested in any kind of tests/investigations (e.g. imaging etc) that you may have ordered. Please only consider the tests/investigations that you ordered yourself. Please tick **all** that apply and put in the date that the test/investigation was ordered:

| | ✓ | |
|---|---|---|
| Chest x-ray | | D D M M Y Y Y Y |
| MRI scan | | D D M M Y Y Y Y |
| CT scan | | D D M M Y Y Y Y |
| PET scan | | D D M M Y Y Y Y |
| Sputum test | | D D M M Y Y Y Y |
| Lung biopsy | | D D M M Y Y Y Y |
| Bronchoscopy | | D D M M Y Y Y Y |
| Other (please specify): | | D D M M Y Y Y Y |



**4. Date of referral to specialist medical services**

At what date did you **first** refer the patient to hospital or another specialist transferring the responsibility for on-going investigation/treatment to other medical services?

D D M M Y Y Y Y

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## 5. Nature of this referral

**5.1 Do you know the date that the patient was seen for this referral?**

☐ **Yes**, please provide the date: D D M M Y Y Y Y

☐ **No**

**5.2 If you did make a referral to specialist services, which of the following best describes the nature/characteristics of this referral?** Please tick **one**.

| | ✓ |
|---|---|
| Emergency admission: a referral to A&E (or equivalent) for immediate admission | |
| An urgent referral for assessment of cancer symptoms/signs/test results (Note this will be within 2 weeks for England/Wales) | |
| A less urgent referral in which cancer is raised as a possibility (Note this will be greater than 2 weeks for England/Wales) | |
| A more general referral for investigation and assessment without cancer mentioned | |
| No referral was made | |
| Other – please describe | |



**5.3 Would you say this patient's diagnostic pathway was conducted predominantly in the public or private system?** Please tick **one**.

| | ✓ |
|---|---|
| Public healthcare system | |
| Private healthcare system | |

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## 6. Date of lung cancer diagnosis

This can be decided in different ways. Please tick **all** that apply.
Please provide whichever of the following dates you have to hand:

| | ✓ | |
|---|---|---|
| Date of histological confirmation [ideal] | | D D M M Y Y Y Y |
| Date results of investigation (histological or other) confirming cancer received | | D D M M Y Y Y Y |
| Date patient was told | | D D M M Y Y Y Y |
| Date biopsy undertaken | | D D M M Y Y Y Y |
| Date patient was first admitted to hospital because of the malignancy | | D D M M Y Y Y Y |
| Other (please specify) | | D D M M Y Y Y Y |

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## 7. Additional information

Finally, we are interested to know what other conditions your patient has, and the severity/impact of these conditions

Have you and/or any of your partners treated this patient (or has the patient been to hospital) for any of the following conditions? Please tick **all** that apply:

| | |
|---|---|
| Cardiovascular disease | ☐ Yes ☐ No |
| Stroke | ☐ Yes ☐ No |
| Lung disease (except lung cancer) | ☐ Yes ☐ No |
| Diabetes | ☐ Yes ☐ No |



**Are there any other comments you would like to make about this patient?**

Name (and title): _____

Signature: _____

Date: _____

**Thank you very much for taking the time to complete this questionnaire.**

A3: Cancer treatment specialists (CTS) questionnaire

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# International Cancer Benchmarking Partnership Module 4

## Specialist Care Audit

## Lung Cancer

Thank you very much for agreeing to fill in this questionnaire – it should take about 10 minutes to complete. As part of an international study examining differences in cancer survival, we are sending the questionnaire to health care providers of a sample of patients with cancer.

Our aim is to gain a better understanding of the process by which people have their cancer diagnosed – the symptoms they experience, and the pathway they follow from onset of symptoms to treatment of their cancer. We hope you can help us with information on this patient's cancer journey once they were referred to specialist cancer services. This will help in identifying ways in which cancers can be diagnosed and treated quickly and effectively.



**Thank you once again for your time**

**Please can you refer to your patient's notes in completing the questionnaire, as this will help in obtaining accurate data on time points.**

If you would prefer to return this questionnaire without the patient details, please tear off along the dotted line.

Your patient _____

is participating in the study.

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**Patient information**

ID-number: Jurisdiction-ID + Patient-ID:

Full name:

Address:

Postcode:

Date of birth: D D M M Y Y Y Y

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1. **Date patient first attended hospital/specialist services related to their cancer diagnosis.** We appreciate this date can at times be difficult to identify, particularly when there have been multiple visits in the lead up to a definitive diagnosis. Put another way, it's the date that the hospital/specialist service assumed responsibility for on-going investigation/treatment for your patient.

Day (optional), month, year

| D | D | M | M | Y | Y | Y | Y |
|---|---|---|---|---|---|---|---|
| | | | | | | | |

2. **How was the patient referred to the hospital/specialist services related to their cancer diagnosis?** Please tick.

Was it through a:

| | ✓ | | ✓ |
|---|---|---|---|
| GP referral | | Referral from respiratory clinic | |
| Medical specialist/Consultant referral | | Other referral – please specify: | |



3. **Where did this first contact/appointment happen?** Please tick.
Which of the following best describes where this first contact/appointment took place?

| | ✓ | | ✓ |
|---|---|---|---|
| Emergency department ('A&E') | | Medical outpatient department, please specify which department | |
| Oncology general outpatient department | | Surgical outpatient department, please specify which department | |
| Other – please specify: | | | |

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## 4. Date of diagnosis

This can be decided in different ways.
Please tick and complete as many of the following dates as possible.

| | ✓ | |
|---|---|---|
| Date of histological confirmation (ideal) | | Day (optional), month, year D D M M Y Y Y Y |
| Date results of investigation confirming cancer received | | Day (optional), month, year D D M M Y Y Y Y |
| Date patient was told | | Day (optional), month, year D D M M Y Y Y Y |
| Date of biopsy | | Day (optional), month, year D D M M Y Y Y Y |
| Date patient was first admitted to hospital because of the malignancy | | Day (optional), month, year D D M M Y Y Y Y |
| Date of MDT confirmation of diagnosis | | Day (optional), month, year D D M M Y Y Y Y |
| Other (please specify): | | Day (optional), month, year D D M M Y Y Y Y |

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## 5. Date treatment for the cancer commenced

Based on your records, when would you say that any treatment specifically targeting the patient's cancer started?

Day (optional), month, year

| D | D | M | M | Y | Y | Y | Y |
|---|---|---|---|---|---|---|---|

## 6. Additional information

Please can you provide any further information on the patient's cancer:

| **TNM**, please tick as appropriate: | |
|---|---|
| 0 | |
| I | |
| IIA | |
| IIB | |
| IIC | |
| IIIA | |
| IIIB | |
| IIIC | |
| IV | |
| Not able to stage | |

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**6.1 Histological subtype:** ✓

| | |
|---|---|
| Squamous cell carcinoma | |
| Adenocarcinoma | |
| Large cell carcinoma | |
| Non-small carcinoma | |
| Small cell carcinoma | |
| Carcinoid | |
| Unclassified | |
| Other (please specify): | |

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## Further comments

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Name (and title):

Signature:

Date:



Are you a ... (please tick below):

| | ✓ |
|---|---|
| Surgeon | |
| Medical Oncologist | |
| Clinical Oncologist | |
| Clinical Nurse Specialist | |
| Other (please specify): | |

**Thank you very much for taking the time to complete this questionnaire.**

## Appendix B:

## Rules for missing, incomplete, multiple response and out of range data

| |
|---|
| 1. Oversampling<br>To handle oversampling in Ontario, include only the first 315 consecutive lung cancer patients; |
| 2. Language/Participation in study/Presence of cancer<br>Exclude patients who checked "No, I don't understand the language" or "I don't want to participate in this study" or "I don't have cancer". |
| 3. Survey responders<br>a) Exclude Patient/PCP/Specialist survey from the analysis, if it was not written by Patient/PCP/Specialist (example: a medical oncologist completed a PCP survey);<br>b) In the case of duplicates, include only the first survey (example: 2 specialists completed surveys for the same patient). |
| 4. Gender<br>Exclude patients with unknown Gender. |
| 5. Age<br>a) Exclude patients with unknown age;<br>b) Exclude patients younger 40 years;<br>c) Use registry data, if Age is reported by both patient and registry. |
| 6. No cancer or Previous cancer in the same organ<br>a) Exclude patients with no cancer based on registry data;<br>b) Exclude patients with previous cancer in the same organ based on data from registry or free-text for Presentation in the patient survey. |
| 7. Date of consent<br>Exclude patients with date of consent which is unknown, before 01.01.2013 or in the future. |
| 8. Multiple responses to Dates<br>If multiple responses were given to the dates (of first symptom; first presentation to primary care; referral; diagnosis; treatment start), then use the earliest date. |
| 9. Order of Dates<br>The dates must be in the following order –<br><br>First symptom; first presentation to Primary Care; referral; diagnosis; treatment start.<br><br>If not, check for mistakes. |

10. Date of first symptom
Date of first symptom is defined as date of first symptom from patient data.

11. Date of first presentation
Date of first presentation to Primary Care is defined as (in the order of declining priority):
a) date of first presentation to Primary Care from PCP data;
b) date of first presentation to Primary Care and A&E from PCP data;
c) date of first presentation to Primary Care from patient data.

12. Date of referral
Date of referral is defined as date of referral from PCP data.

13. Date of diagnosis
*Definition*
a) If Registry reports both date of histological confirmation and date of confirming investigation, then use date of histological confirmation.
b) Date of diagnosis (based on patient data, PCP data, specialist data, registry data) is defined as (in the order of declining priority):
- date of diagnosis from registry;
- date of histological confirmation (from specialist data, PCP data);
- date of biopsy (from specialist data, PCP data);
- date of confirming investigation (from specialist data, PCP data);
- date of first hospital admission (from specialist data, PCP data);
- date of MDT confirmation (from specialist data, PCP data);
- date patient was told (from specialist data, PCP data);
- other date of diagnosis (from specialist data, PCP data, patient data);

Choose a Date from a lower level of hierarchy, if the Date from a higher level is after the Date of consent or more than 9 months (=271 days) before the Date of consent.

*Exclusion criteria*

a) Unknown date of diagnosis;
b) Date of diagnosis is after the date of consent;
c) Date of diagnosis is more than 9 months before the Date of consent.

14. Date of treatment start
a) Date of treatment start from patient data is defined as the earliest of the treatment dates for Surgery, Chemo, Radio and Other;
b) Date of treatment start (based on registry data, specialist data, patient data) is defined as (in the order of declining priority):

- date of treatment start from registry data,
- date of treatment start from specialist data,
- date of treatment start from patient data,
- anticipated date of treatment from patient data.

15. Imputation of missing day in the date

Imputation rules for missing day (given month and year are known):

a) Set missing day to '16';
b) Consider adjacent dates in a backwards order (from "Treatment" to "First symptom"). For each pair of such adjacent dates: If dates are not in a logical order (e.g. "Treatment" is before "Diagnosis"), but month and year are the same in both dates, and the day was imputed to '16' in one of the dates:
- Recode the day imputed earlier to '16' to the day from the adjacent date.

16. Considering time

If patient gave multiple answers to the "How long did you have symptoms before contacting a doctor?" question, then use the option with the shortest time interval.

17. Delay arranging appointment

If patient gave multiple answers to the "How long did it take to get an appointment with PCP?" question, then use the option with the shortest time interval.

18. Duration of symptoms

If PCP gave multiple answers to the "Duration of symptoms" question, then use the option with the shortest time interval.

19. Definition of Presentation

A. *Define Presentation within a Data Source*

1. Review the free-text for Presentation (Patient, PCP sources) and re-code, if possible.
2. If PCP reports 'Other' as Presentation and at least one symptom (or "Duration of Symptoms") or if Patient reports 'Other' as Presentation and at least one symptom (or date of first symptom or "Consider waiting time" or "Delay arranging appointment"), then re-code the Presentation in the corresponding data source to 'Unknown'- option.
3. In the case of multiple Presentation responses (Patient, PCP sources) - use a single option (in the order of declining priority):
   a) 'VisitPCP and AE',
   b) 'VisitPCP´, 'AE´ (if both 'VisitPCP´ and 'AE´ are given, then re-code as 'VisitPCP and AE'),
   c) 'Unknown',
   d) 'Investigation for another problem' ,
   e) 'Other"

B. *Define Presentation from Alternative Data*

If Presentation hasn't been reported in either of data sources, then define it 'Unknown',

if PCP reports at least one symptom (or "Duration of symptoms"); or if Patient reports

at least one symptom (or date of first symptom or "Consider waiting time" or "Delay arranging

appointment");

C. *Define Presentation from Data Source Hierarchy*

1. In all jurisdictions, except Sweden – use Presentation data from (in the order of declining priority):
   a) PCP data;
   b) Patient data;
2. In Sweden – use Presentation data from Patient data.

20. Patient interval

The Patient interval is defined as (in the order of declining priority):

a) "Date of first presentation to Primary Care" (rule 11) minus "Date of first symptom" (rule 10);
b) If the interval in (a) is unknown or negative: Calculate the interval as the low boundary of "Considering time" (rule 16) plus the low boundary of "Delay arranging appointment" (rule 17);
c) If the interval in (a) is unknown or negative and the interval in (b) is unknown: Calculate the interval as the low boundary of "Duration of symptoms interval" (rule 18).

21. Primary Care interval

The Primary Care interval is defined as "Date of referral" (rule 12) minus "Date of first presentation to Primary Care" (rule 11).

22. Diagnostic interval

a) The Diagnostic interval is defined as "Date of diagnosis" (rule 13) minus "Date of first presentation to Primary Care" (rule 11).

23. Treatment interval

The Treatment interval is defined as "Date of treatment start" (rule 14) minus "Date of diagnosis" (rule 13).

24. Total interval

a) The Total interval is defined as "Date of treatment start" (rule 14) minus "Date of first symptom" (rule 10).

25. Range of Time intervals

The time intervals (Patient, Primary Care, Diagnosis, Treatment, Total) must be in range 0-1 year.

If > 1 year: set the interval to 365 days

If negative: set the interval to 0.

26. Number of visits
If patient gave multiple answers to the "Number of visits" questions, then use the option with a fewer number of visits.

27. Specialist waiting time interval
If patient gave multiple answers to the ""How long did it take to get an appointment with specialist?" question, then use the option with the shortest time interval.

28. Type of treatment
If patient ticked both "Yes" and "No" as answers to the "Type of treatment (Surgery, Chemotherapy, Radiotherapy)" questions, then choose "Yes" answer.

29. Health state
If patient gave multiple answers to the "Health state" question, then use the option with a better health condition.

30. Comorbidity
a) If patient ticked both "Yes" and "No" as answers to the "Comorbidity (Heart disease, Stroke, Lung disease, Diabetes)" questions, then choose "Yes" answer;
b) If both patient and PCP report "Comorbidity", then use the PCP Data.

31. Ethnicity
a) If patient didn't report "Ethnicity", then use the information from (in the order of declining priority):
   - "Ethnicity_Other_Details";
   - "Other main language spoken at home";
   - "The main language spoken at home" (only for Victoria);
   - "The main language spoken at home is the chief one for this jurisdiction"="Yes" given "Main language spoken at home is other than the main one for this jurisdiction"="No";

b) Consider Ethnicity as unknown, if answers to the "Ethnicity" question are multiple and belong to
different categories ( 'white', 'Asian', 'black', 'other').

32. Education
If patient gave multiple answers to the "Education" question, then use the option with a higher level of education.

33. Smoking Current
a) If patient ticked both "Yes" and "No" as answers to the "Smoking Current" question, then use "Yes" answer;
b) If patient hasn't ticked neither "Yes" nor "No, then consider this case as Unknown.

34. Smoking Number

If patient reports "SmokingNumber" as text, then re-code using following rules:

a) Where there is a number smoked /day – accept number;
b) Where a range has been given – take the upper value;
c) Where patient has put 10+ or 20+ - capture this as 11 or 21;
d) Where number of cigarettes smoked in the past and currently being smoked are provided - average the numbers;
e) Non entries code as "." ;
f) Non-smokers (eg, "nil", "N/A") are coded as "0".

35. Smoked ever

a) If patient ticked both "Yes" and "No" as answers to the "Smoking ever" question, then use "Yes" answer;
b) If patient hasn't ticked neither "Yes" nor "No": consider it as "Yes", if patient is a current smoker ("Smoking_Current="Yes"") or has specified a number of cigarettes ("SmokingNumber">0). Otherwise consider this case as Unknown.
c) If patient has ticked "No": recode it to "Yes", if patient is a current smoker ("Smoking_Current="Yes").

36. Nature of referral

a) Review free-text for " Nature of referral" (PCP Data) and re-code, if possible;
b) In the case of multiple responses, use a single option as (in the order of declining priority):

- "Referral for immediate admission";
- "Urgent referral";
- "Less urgent referral";
- "General referral" ;
- "No referral";
- "Other".

37. Refer Public or Private

a) If PCP ticked both "Public" and "Private" as answers to the "Refer Public or Private" question, then use "Private" answer;
b) If PCP hasn't ticked neither "Public" nor "Private", then consider this case as Unknown.

38. Type of referral

If specialist gave multiple responses to the "How was the patient referred…" question, then use a single option (in the order of declining priority):

- "Respiratory clinic";
- "Specialist/consultant";
- "PCP";
- "Other".

39. First Attendance Place

If specialist gave multiple responses to the "First Attendance Place" question, then consider this case as Unknown.

40. Stage-TNM

a) If specialist gave multiple responses to the "Stage_TNM" question, then use the highest category;
b) If registry gave multiple responses to the "Stage_TNM", then use a single option (in the order of declining priority):
   - stage at time of diagnosis
   - stage at surgery
   - stage at oncology
c) If "Stage_TNM" is reported by both the specialist and registry, then use the registry data.

## Appendix C: Supplementary Tables

**C 1:** Classification of lung cancer -specific symptoms reported by patients into cancer specific and non- cancer specific

**Cancer specific symptoms**

| |
|---|
| 1 persistent cough |
| 2 chest infection that wouldn't get better |
| 3 coughing up blood-stained phlegm (sputum) |
| 4 breathlessness |
| 5 chest or shoulder pain |
| 6 a hoarse voice |
| 7 difficulty swallowing |
| 8 swelling of lymph nodes (glands) in my neck |
| 9 ends of fingers becoming larger |
| 10 breast and axilla swelling (in men) |

**Non-cancer specific symptoms**

| |
|---|
| 1 a dull ache or sharp pain when I coughed or took a deep breath |
| 2 pain/discomfort under my ribs |
| 3 face swelling |
| 4 blood clots (thrombosis) |
| 5 pins and needles or numbness in fingers |
| 6 weight loss |
| 7 felt sick/vomiting/nausea/loss of appetite |
| 8 fatigue |
| 9 muscle weakness |
| 10 drowsiness, weakness, dizziness or confusion |
| 11 high temperature (fever) of 38C (100.4F) |
| 12 other |

**C2:** Time intervals (days) depicted as median, 75$^{th}$ and 90$^{th}$ centiles for each of the ten jurisdictions. In Sweden, no data was available on primary care interval

| Intervals | Centiles | Wales | Denmark | Sweden | England | N Ireland | Scotland | Manitoba | Ontario |
|---|---|---|---|---|---|---|---|---|---|
| Patient Interval | Number | 181 | 233 | 172 | 213 | 179 | 169 | 133 | 205 |
| | Median | 21 | 14 | 21 | 17 | 18 | 21 | 25 | 22 |
| | 75th centile | 61 | 53 | 61 | 65 | 60 | 60 | 67 | 61 |
| | 90th centile | 216 | 180 | 214 | 205 | 240 | 267 | 180 | 187 |
| Primary Care interval | Number | 110 | 159 | n/a | 147 | 124 | 119 | 80 | 75 |
| | Median | 20 | 7 | | 11 | 13 | 16 | 30 | 29 |
| | 75th centile | 43 | 20 | | 31 | 51 | 35 | 75 | 73 |
| | 90th centile | 91 | 64 | | 73 | 112 | 90 | 138 | 183 |
| Diagnostic interval | Number | 176 | 229 | 165 | 212 | 170 | 173 | 138 | 212 |
| | Median | 45 | 35 | 28 | 54 | 65 | 42 | 87 | 57 |
| | 75th centile | 108 | 67 | 83 | 100 | 122 | 106 | 147 | 122 |
| | 90th centile | 162 | 162 | 143 | 161 | 281 | 198 | 265 | 331 |
| Treatment interval | Number | 192 | 279 | 190 | 238 | 200 | 187 | 182 | 263 |
| | Median | 43 | 16 | 34 | 22 | 32 | 42 | 19 | 47 |
| | 75th centile | 64 | 25 | 59 | 41 | 48 | 62 | 56 | 70 |
| | 90th centile | 89 | 37 | 77 | 56 | 72 | 90 | 97 | 96 |
| Total interval | Number | 147 | 192 | 147 | 176 | 157 | 143 | 117 | 178 |
| | Median | 116 | 67 | 107 | 114 | 105 | 117 | 127 | 130 |
| | 75th centile | 204 | 116 | 190 | 183 | 227 | 253 | 216 | 216 |
| | 90th centile | 365 | 210 | 329 | 323 | 365 | 365 | 365 | 339 |

**C3:** Data sources used to define dates and percentage of imputed dates

| Type of date | Data sources used to define a date* (%) | | | | Cases with imput day in a date** (% |
|---|---|---|---|---|---|
| | Patient | PCP | CST | Registry | |
| First noticing symptoms | 100 | 0 | 0 | 0 | 66 |
| First presentation to health care | 49 | 51 | 0 | 0 | 30 |
| First referral to secondary care | 0 | 100 | 0 | 0 | 1 |
| Diagnosis | 5 | 6 | 8 | 81 | 1 |
| Start of curative or palliative treatment | 55 | 0 | 32 | 13 | 11 |

* based on rules 10-14, supplementary file Appendix B
** based on rule 15, supplementary file Appendix B

**C4.** Percentages of negative intervals set to 0, large intervals (>365 days) set to 365 days, and intervals based not on dates

| Type of interval | Negative intervals set to 0 days* (%) | Intervals >365 days set to 365 days* (%) | Intervals where variables other than dates were used (%)** |
|---|---|---|---|
| Patient | <1 | 5 | 29 |
| Primary care | 4 | 2 | 0 |
| Diagnosis | 6 | 5 | 0 |
| Treatment | 6 | <1 | 0 |
| Total | 2 | 9 | 0 |

* based on rule 25, supplementary file Appendix B
* based on rule 20b,c, supplementary file Appendix B

**The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.**

| | Item No. | STROBE items | Location in manuscript where items are reported | RECORD items | Location in manuscript where items are reported |
|---|---|---|---|---|---|
| **Title and abstract** | | | | | |
| | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found | Title and abstract – p 1 and 3 | RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.<br><br>RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.<br><br>RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract. | Abstract – p 3<br><br>Abstract – p 3<br><br>N/A |
| **Introduction** | | | | | |
| Background rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Introduction – p 6 | | |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Introduction – p 6 | | |
| **Methods** | | | | | |
| Study Design | 4 | Present key elements of study design early in the paper | Methods – p 6 | | |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Methods – p 6-8 | | |
| Participants | 6 | *(a) Cohort study* - Give the eligibility criteria, and the | Methods – p 6 – and as reference to | RECORD 6.1: The methods of study population selection (such as codes or | Provided as reference to |

| | | | | | |
|---|---|---|---|---|---|
| | | sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants<br><br>*(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study* - For matched studies, give matching criteria and the number of controls per case | previous paper.<br><br>N/A | algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.<br><br>RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.<br><br>RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage. | previous paper.<br><br>Provided as appendix and in reference to previous paper.<br><br>N/A |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. | Methods – p 6-9 – and as reference to previous paper. | RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided. | N/A |
| Data sources/ measurement | 8 | For each variable of interest, give sources of data and details of methods of assessment (measurement).<br>Describe comparability of assessment methods if there is more than one group | Methods – p 6-9 – and as reference to previous paper. | | |
| Bias | 9 | Describe any efforts to address potential sources of bias | Methods – p 7-8, discussion – p 24-25 – and as reference to | | |

| | | | | | |
|---|---|---|---|---|---|
| | | | previous paper. | | |
| Study size | 10 | Explain how the study size was arrived at | Methods – p 6 – and as reference to previous paper. | | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | Methods – p 6-8 – and as reference to previous paper. | | |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding<br>(b) Describe any methods used to examine subgroups and interactions<br>(c) Explain how missing data were addressed<br>(d) *Cohort study* - If applicable, explain how loss to follow-up was addressed<br>*Case-control study* - If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy<br>(e) Describe any sensitivity analyses | Methods – p 8 – and as reference to previous paper. | | |
| Data access and cleaning methods | | .. | | RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. | N/A |

| | | | | | |
|---|---|---|---|---|---|
| | | | | RECORD 12.2: Authors should provide information on the data cleaning methods used in the study. | Methods – p 7 |
| Linkage | | .. | | RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided. | N/A |
| **Results** | | | | | |
| Participants | 13 | (a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed)<br>(b) Give reasons for non-participation at each stage.<br>(c) Consider use of a flow diagram | Results and as table – p 10-11. Flow diagram in previous paper, referenced. | RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram. | Results – p 10-15 - and as table. Flow diagram in previous paper, referenced. |
| Descriptive data | 14 | (a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate the number of participants with missing data for each variable of interest<br>(c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount) | Results and as table – p 10-15. | | |
| Outcome data | 15 | *Cohort study* - Report numbers of outcome events or summary measures over time<br>*Case-control study* - Report numbers in each exposure category, or summary measures | Results and as table – p 16-23. | | |

| | | | | | |
|---|---|---|---|---|---|
| | | of exposure<br>*Cross-sectional study* - Report numbers of outcome events or summary measures | | | |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(b) Report category boundaries when continuous variables were categorized<br>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Results and as table – p 21-23. | | |
| Other analyses | 17 | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses | Results – p 23. | | |
| **Discussion** | | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | Discussion – p 24 | | |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Discussion – p24-25 | RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported. | Discussion – p24-25 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar | Discussion – p25-28 | | |

| | | | | | |
|---|---|---|---|---|---|
| | | studies, and other relevant evidence | | | |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | Discussion, conclusion – p25-29. | | |
| **Other Information** | | | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Funding statement – p 31 | | |
| Accessibility of protocol, raw data, and programming code | | .. | | RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code. | Availability of data and material statement – p 31 |

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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# Time intervals and routes to diagnosis for lung cancer in ten jurisdictions: cross-sectional study findings from the International Cancer Benchmarking Partnership (ICBP)

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| | |

**Time intervals and routes to diagnosis for lung cancer in ten jurisdictions: cross-sectional study findings from the International Cancer Benchmarking Partnership (ICBP)**

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## Abstract

### Objective

Differences in time intervals to diagnosis and treatment between jurisdictions may contribute to previously reported differences in stage at diagnosis and survival. The International Cancer Benchmarking Partnership Module 4 (ICBP M4) reports the first international comparison of routes to diagnosis and time intervals from symptom onset until treatment start for lung cancer patients.

### Design

Newly diagnosed lung cancer patients, their primary care physicians (PCP) and cancer treatment specialists (CTS) were surveyed in Victoria (Australia), Manitoba and Ontario (Canada), Northern Ireland, England, Scotland and Wales (UK), Denmark, Norway and Sweden. Using Wales as the reference jurisdiction, the 50$^{th}$, 75$^{th}$ and 90$^{th}$ percentiles for intervals were compared using quantile regression adjusted for age, gender and comorbidity.

### Participants

Consecutive newly diagnosed lung cancer patients, aged >40 years, diagnosed between October 2012 and March 2015 were identified through cancer registries. Of 10,203 eligible symptomatic patients contacted, 2,631 (27.5%) responded and 2,143 (21.0%) were included in the analysis. Data was also available from 1,211 (56.6%) of their PCPs and 643 (37.0%) of their CTS.

### Primary and secondary outcome measures:

Interval lengths (days, primary), routes to diagnosis, symptoms (secondary).

### Results

With the exception of Denmark (-49 days), in all other jurisdictions the median adjusted total interval from symptom onset to treatment, for respondents diagnosed in 2012-15, was similar to that of Wales (116 days). Denmark had shorter median adjusted primary care interval (-11 days) than Wales (20 days); Sweden had shorter (-20) and Manitoba longer (+40) median adjusted diagnostic intervals compared to Wales (45 days). Denmark (-13), Manitoba (-11), England (-9) and Northern Ireland (-4) had shorter median adjusted treatment intervals than Wales (43 days). The differences were greater for the 10% of patients who waited the longest. Based on overall trends, jurisdictions could be grouped into those with trends of reduced,

longer and similar intervals to Wales.The proportion of patients diagnosed following presentation to the PCP ranged from 35-75%.

**Conclusion**

There are differences between jurisdictions in interval to treatment, which are magnified in lung cancer patients who wait the longest. The data could help jurisdictions develop more focused lung cancer policy and targeted clinical initiatives. Future analysis will explore if these differences in intervals impact on stage or survival.

**Key words:**

lung cancer, routes to diagnosis, time intervals, international health systems, symptomatic presentation

**Strengths and limitations of this study**

- This is the first study to use standardized survey methods and definitions to systematically examine key intervals from patients first noticing symptoms or bodily changes until the start of treatment for lung cancer across multiple jurisdictions
- Recall bias was minimised by the triangulation of different data sources and by patients completing the questionnaire within a limited time window (median 5 months) after the cancer diagnosis
- A key limitation, as with all questionnaire-based studies was selection and non-response bias which varied across jurisdictions
- Recruitment of patients up to 9 rather than 6 months after diagnosis might have magnified selection bias due to high mortality in lung cancer but a sensitivity analysis suggests that this did not impact on the results.
- The comparisons for Norway and Victoria, are limited by small sample size and inclusion of only surgical patients, respectively.

## Introduction

Lung cancer is the most common cancer worldwide, with nearly 1.83 million cases diagnosed in 2012, and is the leading cause of cancer death globally, accounting for 19% of cancer deaths.[1] Survival is typically low, with 5-year survival in Europe,North America and Australia <20%.[2-3] A key factor is diagnosis at advanced stage. Reasons for this are multi-faceted and include delays due to the atypical nature of some presenting symptoms, poor sensitivity of chest X-rays and physicians not acting quickly enough.[4] Within European countries, differences of 12 and 5 percentage points in 1- and 5-year relative survival, respectively, have been reported for lung cancers diagnosed between 1999-2007.[5] This and other international comparisons raises the possibility of additional contributory factors such as variations in referral patterns, access to diagnostic tests and delays in treatment.[6]

One way of addressing this is to chart the patient journey from first noticing symptoms to treatment start. Many national studies using different methodologies have reported on time intervals to treatment of lung cancer and there are reviews that have looked at international timeframe comparisons [7-10] [11-24] However, as far as we are aware there is no study that has undertaken international comparisons of timeliness across multiple countries using the same methodology.

The International Cancer Benchmarking Partnership (ICBP) was established to explore differences in cancer outcomes and their causes in countries with comparable wealth and universal access to healthcare.[25] We report results from Module 4 (ICBP M4) on differences in time intervals and routes to diagnosis in symptomatic lung cancer patients from ten jurisdictions in Australia, Canada, Denmark, Norway, Sweden and the United Kingdom.

## Methods

Methods have been previously detailed.[26] In brief, in each of the ten participating jurisdictions (Victoria (Australia), Manitoba, Ontario (Canada), Denmark, Norway, Sweden Northern Ireland, England, Scotland and Wales), consecutive patients aged ≥40 years, newly diagnosed with malignant lung or bronchus cancer (ICD-10:C34.0-C34.9; ICD-O-3 behaviour code /3) were identified by the cancer registry using validated methods (hospital episode, cancer registration, pathology). Exclusion criteria included previous lung or synchronous cancers. Patients with a previous non-lung primary cancer were eligible. Target recruitment was 200 symptomatic patients per jurisdiction.

Following a vital status check, cancer registries posted the patient questionnaire (Appendix A1) either 1) to the relevant primary care physician (PCP) who then forwarded the pre-

addressed envelope to the patient after confirmation that the person was aware of the diagnosis and not deemed too sick/anxious to participate in the survey. (Wales, England, Scotland) or 2) to the patient directly or via the research team (remaining seven jurisdictions). In an attempt to decrease attrition and recall bias, the protocol initially specified that all patient questionnaires should be completed within 6 months of diagnosis. As there were administrative delays in cancer notification, this was extended to 9 months.

On receipt of a completed patient questionnaire, in all jurisdictions except Sweden, the relevant PCP and cancer treatment specialist (CTS) were sent questionnaires (Appendix A.2 and A.3). Specialists provided information on diagnosis and start date of treatment. The latter was collected directly from registry records in Northern Ireland and clinical databases in Denmark. Manitoba did not provide specialist data. Date of diagnosis and stage was also collected where possible through cancer registries. Information on the types of treatment (surgery, chemotherapy, radiotherapy and other) were obtained from the patient survey.

*Data handling*

Data were recoded centrally to ensure that the same explicit rules were applied throughout. Patients in whom age, date of diagnosis or consent were missing were excluded from analyses. Rules were used to combine data from the different sources in a standardised way that ensured reproducibility and transparency (Appendix B). The rules employed a 'hierarchy' principle in terms of the order in which different data sources were used and included imputation rules based on the available data. The exact rule was guided by the measure in question – for example, patient interval was collected primarily from the patient questionnaire whereas primary care time-points from the PCP questionnaire. We applied rules for outliers and implausible measures (e.g. negative time intervals were recorded to zero-days and intervals longer than a year to 365 days).

*Routes to diagnosis and symptoms prompting physician visit*

These were derived from patient and PCP responses. Symptoms were coded by two PCP authors (DW and PV) into 'lung cancer specific' or 'other' (Appendix C1).

*Time intervals*

Time intervals were derived using the checklist for the Aarhus Statement.[27] The following time-points were used to calculate the corresponding time intervals (Figure 1):

- first noticing symptoms
- first presentation to health care
- first referral to secondary care

- diagnosis date
- start of curative or palliative treatment

FIGURE 1

All time-points were validated if there were obvious inconsistencies and negative intervals were set to 0 days. All intervals were truncated at 365 days. Missing data were imputed based on specific rules to ensure that the direction of a possible misclassification bias was known.

*Demographics*

Health status was measured using the self-reported general health item from short form 36 health survey (SF36).[28] Comorbidity was defined as one of four patient or PCP-reported diseases (heart or lung disease, stroke or diabetes) and categorised into: 'none', 'medium' (one or two) or 'high' (three or four). Level of educational was categorised as 'low' (vocational school or lower) and 'high' (university). Stage data (tumour, node, metastasis - TNM - classification) was grouped as I, II, III, IV or missing.[29]

*Statistical analysis*

Patient characteristics across jurisdictions were compared using Kruskal-Wallis test for continuous and ordinal data. For nominal data we used Pearson's chi-squared test and Fisher's exact test (if more than 20% of expected cell counts were less than 5 or at least one expected cell count was 0). The differences in intervals between the jurisdictions were estimated using quantile regression, as this method allows for a comparison across the whole distribution of length of the interval.[30] As we were interested in a measure of central tendency of length of the interval and in long and very long intervals, the focus of the study was on the $50^{th}$(median), $75^{th}$ and $90^{th}$ interval percentiles. Wales was chosen as the reference jurisdiction as it had the lowest lung cancer survival in ICBP Module 1 analysis.[10] Since the length of the interval in days is a continuous measure which has been rounded, we applied the quantile regression analysis on the smoothed quantiles; the method based on the smoothed quantiles is recommended for analyses of discrete (count) data [31]. In STATA this method is implemented in the 'qcount' procedure.[32] Parameters were calculated with 1000 jittered samples. For all interval analyses, the differences in intervals were calculated as marginal effects after quantile regression by setting the continuous covariate (age) to their mean values and the categorical covariates (sex and comorbidity) to their modes. Significance level was set to $\leq 0.05$ with 95% confidence intervals (95%CI) calculated where appropriate. Statistical analyses were carried out using STATA v14.

*Sensitivity and validity analyses*

All analyses were repeated using only (1) those who fulfilled the 6-month cut-off criteria for interval from diagnosis to questionnaire completion and (2) patient data. The effect of excluding patients for whom at least one interval was missing was investigated.We also repeated the analysis after omitting time intervals which were negative or over 365 days. Agreement between the different data sources (registry, patient, PCP (except in Sweden) and CTS (except in Sweden and Manitoba) was measured by Lin's concordance correlation coefficient (CCC).[33]

*Patient involvement*

The research questions for this survey drew on an extensive literature relating to diagnosis and treatment delays leading to negative patient experiences. While patient experience was not a primary outcome measure for this study, patients were given the opportunity to comment on their experience through questionnaire free-text response options (under separate analysis). Patients were involved in the piloting of study instruments to ascertain if recruitment and questionnaire content and dissemination strategies were appropriate, described elsewhere.[26] Each jurisdiction has committed to communicating the findings and local implications of this study to organisations representing their study participants.

**Results**

Of 14,583 lung cancer patients, diagnosed between October 2012 and March 2015 who were alive when identified, 70% (10,203/14,583) were contacted (Table 1). Of 4380 not contacted, 3367 (77%) were from England, Wales and Scotland. Major reasons reported by the PCP for not forwarding the survey included patients being terminally ill, not aware of cancer diagnosis at the time of request, having cognitive or visual impairment, language / communication difficulties, no longer at the address, not wishing to take part in research and a handful not having the index cancer. In addition patents identified were not contacted in England as the target recruitment had been exceeded. For the non-UK jurisdictions, the main reasons for not contacting patients were the patient having died or no longer at the address.

2,631 (27.5% of contacted, 18% of eligible) completed the patient questionnaire at a median of 5 months (range: 0.1,9) after diagnosis (Table 2). The response rate of contacted patients varied from 11.1% (146/1318) in Norway to 61.8% (333/539) in Denmark. Responding patients were more likely to be aged 60-79 years with less advanced stage (Table 1) and alive one year post diagnosis (data not shown). Of the 2,631 responses, 2,143 (81.5%) were included in the analyses which equates to 14.7% (2,143/14,583) of eligible patients. The key reason respondents were excluded were local oversampling (43.9%; 214/488) for additional analyses

(Table 1). In Victoria, the registry was only able to contact patients who had undergone surgery while the sample size in Norway was limited (n=88) due to delays in securing appropriate approvals.

**Table 1:** Cohort for all ten jurisdictions and overall

| Jurisdiction | Patients approached via PCP | | | | | | Patient approached directly by registries/research teams | | | | | | | | | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Wales | | England | | Scotland | | N Ireland | | Denmark | | Manitoba | | Ontario | | Sweden | | Norway | | Victoria | | | |
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| **Eligible patients** [a, b] | **1,811** | **(100)** | **2,517** | **(100)** | **1,366** | **(100)** | **620** | **(100)** | **539** | **(100)** | **980** | **(100)** | **4,080** | **(100)** | **493** | **(100)** | **1,318** | **(100)** | **859** | **(100)** | **14,583** | **(100)** |
| **Packs sent to PCP** [c, d] | **1,811** | **(99.7)** | **1,759** | **(69.9)** | **1,137** | **(83.2)** | | | | | | | | | | | | | | | **4,707** | **(82.7)** |
| pack not forwarded by PCP | 547 | (30.1) | 255 | (14.5) | 201 | (17.7) | | | | | | | | | | | | | | | 1,003 | (21.3) |
| unsure if pack forwarded by PCP | 531 | (29.2) | 559 | (31.8) | 234 | (20.6) | | | | | | | | | | | | | | | 1,324 | (28.1) |
| **Patients contacted by PCP** [c, d] | **733** | **(40.4)** | **945** | **(53.7)** | **702** | **(61.7)** | | | | | | | | | | | | | | | **2,380** | **(50.6)** |
| **Patients approached directly** [c] | | | | | | | **614** | **(99.0)** | **539** | **(100)** | **745** | **(76.0)** | **3,687** | **(90.4)** | **493** | **(100)** | **1,200** | **(91)** | **545** | **(63.4)** | **7,823** | **(88)** |
| patient died | | | | | | | 6 | (1.0) | 0 | (0.0) | 103 | (13.8) | 249 | (6.8) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 358 | (4.6) |
| no address | | | | | | | 0 | (0.0) | 0 | (0.0) | 9 | (1.2) | 255 | (6.9) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 264 | (3.4) |
| Other | | | | | | | 0 | (0.0) | 0 | (0.0) | 6 | (0.8) | 215 | (5.8) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 221 | (2.8) |
| **Patient responses (% of eligible patients)**[c] | **223** | **(12.3)** | **261** | **(10.4)** | **235** | **(17.2)** | **226** | **(36.5)** | **333** | **(61.8)** | **205** | **(20.9)** | **572** | **(14.0)** | **217** | **(44)** | **146** | **(11.1)** | **213** | **(24.8)** | **2,631** | **(18)** |
| **Patient responses (% of contacted)**[e] | **223** | **(30.4)** | **261** | **(27.6)** | **235** | **(33.5)** | **226** | **(37.2)** | **333** | **(61.8)** | **205** | **(32.7)** | **572** | **(19.3)** | **217** | **(44)** | **146** | **(12.2)** | **213** | **(39.1)** | **2,631** | **(27.5)** |
| extra sample for local purpose | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 214 | (37.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 214 | (8.1) |
| other | 0 | (0.0) | 0 | (0.0) | 35 | (14.9) | 25 | (11.1) | 38 | (11.4) | 0 | (0.0) | 43 | (7.5) | 0 | (0.0) | 0 | (0.0) | 3 | (1.4) | 144 | (5.5) |
| **Patient surveys submitted for analyses** [f] | **223** | **(100)** | **261** | **(100)** | **200** | **(85.1)** | **201** | **(88.9)** | **295** | **(88.6)** | **205** | **(100)** | **315** | **(55.1)** | **217** | **(100)** | **146** | **(100)** | **210** | **(98.6)** | **2,273** | **(86.4)** |
| excluded for analyses – total | 12 | (5.4) | 9 | (3.4) | 2 | (1.0) | 1 | (0.5) | 10 | (3.4) | 3 | (1.5) | 27 | (8.6) | 6 | (2.8) | 58 | (39.7) | 2 | (1.0) | 130 | (5.7) |
| - previous cancer | 0 | (0.0) | 5 | (1.9) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 3 | (1.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 8 | (0.4) |
| - unknown date of consent or diagnosis | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 5 | (1.7) | 0 | (0.0) | 1 | (0.3) | 6 | (2.8) | 4 | (2.7) | 0 | (0.0) | 16 | (0.7) |
| - consent too late/too early | 12 | (5.4) | 4 | (1.5) | 2 | (1.0) | 1 | (0.5) | 5 | (1.7) | 3 | (1.5) | 22 | (7.0) | 0 | (0.0) | 33 | (22.6) | 2 | (1.0) | 84 | (3.7) |
| - other | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) | 0 | (0.0) | 21 | (14.4) | 0 | (0.0 | 22 | (1.0) |
| **Patients included in analyses** [i] **(% of forwarded surveys)** | **211** | **(94.6)** | **252** | **(96.6)** | **198** | **(99.0)** | **200** | **(99.5)** | **285** | **(96.6)** | **202** | **(98.5)** | **288** | **(91.4)** | **211** | **(97.2)** | **88** | **(60.3)** | **208** | **(99.0)** | **2,143** | **(94.3)**[h] |
| **PCP surveys** [j] **(% of analysed patients)** | **133** | **(63.0)** | **196** | **(77.8)** | **149** | **(75.3)** | **181** | **(90.5)** | **218** | **(76.5)** | **109** | **(54.0)** | **93** | **(32.5)** | **n/a** [h] | | **27** | **(30.7)** | **105** | **(50.5)** | **1,211** | **(56.6)**[i] |
| **Specialist surveys** [k] **(% of analysed patients)** | **98** | **(46.4)** | **153** | **(60.7)** | **106** | **(53.5)** | **n/a** [g] | | **149** [g] | **(52.3)** | **n/a** [h] | | **62** | **(21.7)** | **n/a** [h] | | **20** | **(22.7)** | **55** | **(26.4)** | **643** | **(37.0)**[m] |

[a]Eligible as per protocol: individual aged 40 years or more, with cancer of the lung or bronchus (ICD-10 code: C34.0-C34.9; behaviour code ICD-O 3) but no synchronous primary cancer or prior history of lung cancer, alive at identification who completed consent to participate within nine months of diagnosis. [b]In some jurisdictions some 'eligible' patients had pre-opted out from being contacted and a small number where PCP information was not available. [c]Percentages of eligible patients. [d]Maximum of potentially contacted patients. i.e. sum of packs forwarded by PCP and packs unsure if forwarded by PCP. [e]Percentages of patients contacted by PCP (see note d) for Wales, England and Scotland or percentages of patients contacted directly by a registry; excl. non-accessible patients due to death or no patient addresses (all other jurisdictions). [f]Percentages of patient responses. [g]Data obtained from registries instead in N Ireland and Denmark. [h]Data not collected in this jurisdiction. [i]Denominator = total number of forwarded cases excl. patients not included in analytic sample in Ontario. [j]Denominator r = total number of analysed cases excl. patients from Sweden. [k]Denominator = total number of analysed cases excl. patients from Sweden. Manitoba & N Ireland

*Baseline characteristics*

Patient characteristics are detailed in Table 2. The cohort was predominantly White (95%), median age 70 years (IQR 64,75) with 82% reporting 'low' levels of education. Norway provided stage data classified as local, regional and distant which could not be converted to TNM stage data.

Ontario was the only jurisdiction with more female (65%) than male respondents. While self-reported health differed significantly, with Welsh patients (9%) reporting twice as high 'poor health' rates than English or Swedish (4%) and eight-fold that of Manitoba (2%), there was no difference in self-reported comorbidity rates. Even after the exclusion of Victoria, there was significant variation in early Stage (I/II) disease which ranged from 25% (Wales) to 59% (Ontario) and surgical resection rates which varied from 27% (Wales) to 58% (Ontario) (Table 2).

**Table 2.** The characteristics of eligible patients by jurisdictions and overall

| | Wales (N=211) | England (N=252) | Scotland (N=198) | N Ireland (N=200) | Denmark (N=285) | Manitoba (N=202) | Ontario (N=288) | Sweden (N=211) | Norway (N=88) | Victoria (N=208) | Overall (N=2143) | p-value[6] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Date of diagnosis of first patient | 03/04/2013 | 28/01/2013 | 26/04/2013 | 22/01/2013 | 16/05/2013 | 10/10/2012 | 08/10/2013 | 01/10/2013 | 16/01/2014 | 08/01/2013 | 10/10/2012 | |
| Date of diagnosis of last patient | 25/09/2014 | 14/08/2013 | 04/12/2013 | 02/12/2014 | 13/11/2013 | 27/03/2015 | 01/10/2014 | 30/05/2014 | 21/01/2015 | 28/12/2014 | 27/03/2015 | |
| Interval from diagnosis date of first patient to last patient in months (recruitment period) | 18 | 7 | 7 | 23 | 6 | 30 | 12 | 8 | 12 | 24 | 30 | |
| Median (range) interval diagnosis to questionnaire completion in months | 5 (0.6,9) | 5 (3,9) | 5 (1,9) | 4 (0.1,9) | 5 (2,8) | 6 (4,9) | 6 (4,9) | 4 (3,8) | 7 (5,9) | 5 (0.2,8) | 5 (0.1,9) | |
| **Age** years Median (IQR) | 71 (65, 77) | 71 (65, 77) | 70 (64, 76) | 69 (62, 75) | 70 (63, 74) | 70 (63, 77) | 70 (64, 75) | 70 (63, 75) | 69 (64, 73) | 68 (63, 73) | 70 (64, 75) | 0.010[1] |
| **Sex** n(%) Male | 127(60) | 134(53) | 100(51) | 105(53) | 151(53) | 100(50) | 131(45) | 111(53) | 46(52) | 112(54) | 1117(52) | 0.159[2] |
| **Health State** n(%) Good | 135(64) | 176(70) | 131(66) | 126(63) | 190(67) | 156(77) | 220(76) | 152(72) | 50(57) | 163(78) | 1499(70) | <0.001*[1] <0.001**[2] |
| Fair | 55(26) | 59(23) | 52(26) | 51(26) | 62(22) | 41(20) | 47(16) | 49(23) | 32(36) | 33(16) | 481(22) | |
| Poor | 20(9) | 11(4) | 14(7) | 16(8) | 18(6) | 4(2) | 16(6) | 9(4) | 6(7) | 10(5) | 124(6) | |
| Missing | 1(0.5) | 6(2) | 1(0,5) | 7(4) | 15(5) | 1(0.5) | 5(2) | 1(0.5) | 0(0) | 2(1) | 39(2) | |
| **Comorbidity**[3] n(%) No | 92(44) | 113(45) | 98(49) | 82(41) | 111(39) | 101(50) | 136(47) | 114(54) | 35(40) | 98(47) | 980(46) | 0.029*[1] 0.032**[2] |
| Medium | 111(53) | 129(51) | 92(46) | 103(52) | 157(55) | 93(46) | 132(46) | 87(41) | 48(55) | 100(48) | 1052(49) | |
| High | 7(3) | 9(4) | 8(4) | 15(8) | 11(4) | 6(3) | 18(6) | 6(3) | 5(6) | 8(4) | 93(4) | |
| Missing | 1(0.5) | 1(0.4) | 0(0) | 0(0) | 6(2) | 2(1) | 2(0.7) | 4(2) | 0(0) | 2(1) | 18(0.8) | |
| **Education** n(%) Low | 172(82) | 217(86) | 174(88) | 166(83) | 232(81) | 170(84) | 224(78) | 159(75) | 65(74) | 181(87) | 1760(82) | <0.001*[1] <0.001**[2] |
| High | 11(5) | 15(6) | 11(6) | 17(9) | 15(5) | 21(10) | 55(19) | 48(23) | 14(16) | 24(12) | 231(11) | |

| | Wales (N=211) | England (N=252) | Scotland (N=198) | N Ireland (N=200) | Denmark (N=285) | Manitoba (N=202) | Ontario (N=288) | Sweden (N=211) | Norway (N=88) | Victoria (N=208) | Overall (N=2143) | p-value[6] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Missing | 28(13) | 20(8) | 13(7) | 17(9) | 38(13) | 11(5) | 9(3) | 4(2) | 9(10) | 3(1) | 152(7) | |
| **Ethnicity** n(%) White | 205(97) | 249(99) | 197(99) | 196(98) | 267(94) | 173(86) | 261(91) | n/a | 87(99) | 199(96) | 1834(95) | <0.001*[2] <0.001**[2] |
| Asian | 1(0.5) | 0(0) | 1(0.5) | 0(0) | 0(0) | 12(6) | 21(7) | n/a | 1(1) | 6(3) | 41(2) | |
| Black | 0(0) | 1(0.4) | 0(0) | 0(0) | 1(0.4) | 0(0) | 1(0.3) | n/a | 0(0) | 0(0) | 3(0.2) | |
| Other | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 15(7) | 2(0.7) | n/a | 0(0) | 0(0) | 17(0.9) | |
| Missing | 5(2) | 2(0.8) | 0(0) | 4(2) | 17(6) | 2(1) | 3(1) | n/a | 0(0) | 3(1) | 36(2) | |
| **Smoking** n(%) Never | 13(6) | 18(7) | 12(6) | 19(10) | 15(5) | 22(11) | 31(11) | 41(19) | 11(13) | 33(16) | 215(10) | <0.001*[2] <0.001**[2] |
| Currently | 19(9) | 28811) | 26(13) | 41(21) | 58(20) | 24(12) | 29(10) | 29(14) | 11(13) | 9(4) | 274(13) | |
| In the past | 174(82) | 204(81) | 160(81) | 137(69) | 205(72) | 156(77) | 225(78) | 139(66) | 66(75) | 165(79) | 1631(76) | |
| Missing | 5(2) | 2(0.8) | 0(0) | 3(2) | 7(2) | 0(0) | 3(1) | 2(0.9) | 0(0) | 1(0.5) | 23(1) | |
| **Tumour stage – TNM** n(%) I | 26(12) | 68(27) | 49(25) | 42(21) | 74(26) | 83(41) | 133(46) | 59(28) | 3(3) | 124(60) | 661(31) | <0.001*[1] <0.001**[2] |
| II | 27(13) | 36(14) | 32(16) | 33(17) | 26(9) | 19(9) | 38(13) | 11(5) | 5(6) | 47(23) | 274(13) | |
| III | 64(30) | 57(23) | 56(28) | 59(30) | 84(29) | 48(24) | 54(19) | 40(19) | 5(6) | 19(9) | 486(23) | |
| IV | 62(29) | 80(32) | 50(25) | 62(31) | 94(33) | 48(24) | 54(19) | 94(45) | 3(3) | 13(6) | 560(26) | |
| Missing | 32(15) | 11(4) | 11(6) | 4(2) | 7(2) | 4(2) | 9(3) | 7(3) | 72(82)[4] | 5(2) | 162(8) | |
| **Tumour stage – TNM**[5] n(%) I/II | 53(25) | 104(41) | 81(41) | 75(38) | 100(35) | 102(51) | 171(59) | 70(33) | 8(9) | *171(82)* | 764(39) | <0.001*[2,5] <0.001**[2,5] |
| III/IV | 126(60) | 137(54) | 106(54) | 121(61) | 178(62) | 96(48) | 108(38) | 134(64) | 8(9) | 32(15) | 1014(52) | |
| Missing | 32(15) | 11(4) | 11(6) | 4(2) | 7(2) | 4(2) | 9(3) | 7(3) | 72(82) | 5(2) | 157(8) | |
| **Treatment Surgery** n(%) Yes | 57(27) | 107(42) | 84(42) | 65(33) | 81(28) | 113(56) | 168(58) | 65(31) | 36(41) | 199(96) | 975(45) | <0.001*[2,5] <0.001**[2,5] |
| No | 61(29) | 56(22) | 55(28) | 94(47) | 90(32) | 44(22) | 111(39) | 79(37) | 28(32) | 5(2) | 623(29) | |
| Missing | 93(44) | 89(35) | 59(30) | 41(21) | 114(40) | 45(22) | 9(3) | 67(32) | 24(27) | 4(2) | 545(25) | |
| **Treatment Chemo** n(%) Yes | 105(50) | 125(50) | 98(49) | 93(47) | 159(56) | 93(46) | 107(37) | 133(63) | 50(57) | 63(30) | 1026(48) | <0.001*[2,5] <0.001**[2,5] |
| No | 41(19) | 51(20) | 46(23) | 65(33) | 45(16) | 62(31) | 172(60) | 37(18) | 18(20) | 137(66) | 674(32) | |
| Missing | 65(31) | 76(30) | 54(27) | 42(21) | 81(28) | 47(23) | 9(3) | 41(19) | 20(23) | 8(4) | 443(21) | |
| **Treatment Radio** n(%) Yes | 82(39) | 68(27) | 76(38) | 72(36) | 114(40) | 81(40) | 98(34) | 70(33) | 41(47) | 29(14) | 731(34) | <0.001*[2,5] <0.001**[2,5] |
| No | 50(24) | 72(29) | 50(25) | 77(39) | 69(24) | 71(35) | 180(63) | 69(33) | 22(25) | 155(75) | 815(38) | |
| Missing | 79(37) | 112(44) | 72(36) | 51(26) | 102(36) | 50(25) | 10(3) | 72(34) | 25(28) | 24(12) | 597(28) | |
| **Treatment Other** n(%) Yes | 10(5) | 14(6) | 14(7) | 11(6) | 30(11) | 18(9) | 9(3) | 0(0) | 7(8) | 16(8) | 129(6) | <0.001*[2,5] <0.001**[2,5] |

| | Wales (N=211) | England (N=252) | Scotland (N=198) | N Ireland (N=200) | Denmark (N=285) | Manitoba (N=202) | Ontario (N=288) | Sweden (N=211) | Norway (N=88) | Victoria (N=208) | Overall (N=2143) | p-value[6] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No | 48(23) | 63(25) | 45(23) | 69(35) | 255(89) | 3(1) | 261(91) | 0(0) | 2(2) | 138(66) | 884(41) | |
| Missing | 153(72) | 175(69) | 139(70) | 120(60) | 0(0) | 181(90) | 18(6) | 211(100) | 79(90) | 54(26) | 1130(53) | |

[1]Differences between jurisdictions were tested by the Kruskal-Wallis test, [2] Differences between jurisdictions were tested by the Pearson's Chi[2] test, [3]Comorbidity coded as none=no reported, medium=1-2 reported and high=3+ reported, [4] This included cases which could not be mapped as they were classified as per Cancer Registry of Norway into local (stage I), regional (stage II-III) and distant (stage IV) [5]Excluding Victoria, [6]Excluding Norway, *Missing category is excluded, **Missing category is included,
Abbreviations: IQR=inter-quartile range.

*Routes to diagnosis*

Results are detailed in Table 3. Over half (55%) were diagnosed following presentation to the PCP of whom 63% (range: 29% Norway - 82% Wales; data not shown) were urgently referred with a suspicion of cancer, based on the PCP questionnaire.

**Table 3.** Routes to diagnosis of lung cancer patients for each jurisdiction. All figures are n(%) unless otherwise stated.

| | Wales (N=211) | England (N=252) | Scotland (N=198) | N Ireland (N=200) | Denmark (N=285) | Manitoba (N=202) | Ontario (N=288) | Sweden (N=211) | Norway (N=88) | Victoria (N=208) | Total (N=2143) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Symptoms prompting visit to PCP | 109(52) | 150(60) | 128(65) | 131(66) | 170(60) | 101(50) | 91(32) | 65(31) | 35(40) | 106(51) | 1086(51) |
| Symptoms prompting emergency (A&E) department visit[1] | 11(5) | 18(7) | 12(6) | 22(11) | 21(7) | 25(12) | 39(14) | 18(9) | 3(3) | 6(3) | 175(8) |
| Symptoms prompting visit to PCP and emergency (A&E) department[1] | 10(5) | 4(2) | 7(4) | 18(9) | 8(3) | 15(7) | 12(4) | 8(4) | 5(6) | 3(1) | 90(4) |
| Incidental diagnosis in course of investigation/treatment for another problem[2] | 68(32) | 37(15) | 36(18) | 19(10) | 55(19) | 57(28) | 116(40) | 107(51) | 32(36) | 90(43) | 617(29) |
| Unknown routes to diagnosis[3] | 10(5) | 17(7) | 11(6) | 5(3) | 16(6) | 4(2) | 14(5) | 11(5) | 8(9) | 0(0) | 96(5) |
| Other[4] | 3(1) | 25(10) | 3(2) | 4(2) | 14(5) | 0(0) | 16(6) | 2(1) | 5(6) | 3(1) | 75(3) |
| Missing | 0(0) | 1(0.4) | 1(0.5) | 1(0.5) | 1(0.4) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 4(0.2) |

[1] Emergency (A&E) route was ascribed when the patient reported pathway to cancer diagnosis involving going or being taken to the emergency department or the PCP reported that the patient presented to emergency department with or without their involvement [2] this could be by PCP, another doctor or via hospital; [3]includes cases where PCP or patient reported routes to diagnosis as 'Other' or 'Missing' but also reported symptoms or duration of symptoms, or date of first symptom, or waiting time for PCP appointment; [4]includes cases where PCP or patient reported routes to diagnosis as 'Other' and hasn't reported any symptoms or duration of symptoms, or date of first symptom, or waiting time for PCP appointment.

*Symptoms prompting visit to physician*

The median number of patient-reported symptoms were 2 (IQR 1,3). Across jurisdictions, the most common patient-reported symptoms were persistent cough (39%), breathlessness (37%) and fatigue (27%) although there was significant variation in proportion of patients presenting with individual symptoms (Table 4).

The PCPs reported a median of 1 (IQR 1,2) symptom at first presentation, with the most common being persistent cough (39%). Across jurisdictions, the reporting of other symptoms by the PCP was significantly lower compared to patients, especially fatigue (4%) and weight loss (8%). When the analysis was restricted to the cohort where both patient and PCP had completed the survey, this difference persisted. Unlike patients, there was minimal variation in PCP reporting of symptoms, with significant differences limited to 'no symptoms', 'other symptoms not previously listed' and weight loss. Overall 64% of symptoms were labelled as 'cancer specific' by the study PCPs (Table 4).

**Table 4.** Symptoms experienced by patients and presenting symptoms noted by PCP for eligible patients. All figures are n(%)

| | Wales | England | Scotland | N Ireland | Denmark | Manitoba | Ontario | Sweden | Norway | Victoria | Overall | p[1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Symptoms (reported by patient)** | (N=211) | (N=252) | (N=198) | (N=200) | (N=285) | (N=202) | (N=288) | (N=211) | (N=88) | (N=208) | (N=2143) | |
| persistent cough | 113(54) | 123(49) | 97(49) | 83(42) | 97(34) | 71(35) | 125(43) | 84(40) | 10(11) | 39(19) | 842(39) | <0.001 |
| breathlessness | 109(52) | 126(50) | 82(41) | 73(37) | 99(35) | 63(31) | 119(41) | 77(36) | 12(14) | 24(12) | 784(37) | <0.001 |
| fatigue | 75(36) | 79(31) | 64(32) | 61(31) | 38(13) | 55(27) | 92(32) | 60(28) | 17(19) | 42(20) | 583(27) | <0.001 |
| weight loss | 38(18) | 39(15) | 44(22) | 37(19) | 41(14) | 29(14) | 36(13) | 34(16) | 9(10) | 20(10) | 327(15) | 0.147 |
| felt sick /vomiting /nausea/loss of appetite | 42(20) | 33(13) | 31(16) | 24(12) | 33(12) | 22(11) | 45(16) | 28(13) | 3(3) | 20(10) | 281(13) | 0.132 |
| coughing up blood-stained phlegm (sputum) | 35(17) | 32(13) | 24(12) | 31(16) | 21(7) | 16(8) | 27(9) | 25(12) | 5(6) | 23(11) | 239(11) | 0.014 |
| chest or shoulder pain | 23(11) | 9(4) | 18(9) | 24(12) | 10(4) | 28(14) | 43(15) | 25(12) | 4(5) | 22(11) | 206(10) | <0.001 |
| other symptoms not listed above | 51(24) | 80(32) | 59(30) | 54(27) | 63(22) | 40(20) | 30(10) | 75(36) | 26(30) | 42(20) | 520(24) | <0.001 |
| no symptoms | 29(14) | 24(10) | 32(16) | 21(11) | 63(22) | 50(25) | 67(23) | 36(17) | 33(38) | 75(36) | 430(20) | <0.001 |
| missing | 1(0.5) | 16(6) | 6(3) | 17(9) | 31(11) | 9(4) | 4(1) | 4(2) | 12(14) | 1(0.5) | 101(5) | <0.001 |
| **Presenting symptom (reported by PCP)** | (N=85) | (N=133) | (N=115) | (N=0) | (N=151) | (N=86) | (N=61) | (N=0) | (N=17) | (N=81) | (N=729) | |
| persistent cough | 33(39) | 57(43) | 45(39) | n/a | 67(44) | 24(28) | 18(30) | n/a | 7(41) | 33(41) | 284(39) | 0.093 |
| breathlessness | 17(20) | 27(20) | 20(17) | n/a | 27(18) | 11(13) | 11(18) | n/a | 4(24) | 13(16) | 130(18) | 0.803 |
| fatigue | 1(1) | 5(4) | 3(3) | n/a | 9(6) | 2(2) | 2(3) | n/a | 1(6) | 3(4) | 26(4) | 0.539[2] |
| weight loss | 5(6) | 9(7) | 15(13) | n/a | 19(13) | 3(3) | 2(3) | n/a | 0(0) | 5(6) | 58(8) | 0.027 |
| felt sick /vomiting /nausea/loss of appetite | 1(1) | 1(0.8) | 2(2) | n/a | 6(4) | 2(2) | 0(0) | n/a | 0(0) | 0(0) | 12(2) | 0.418[2] |
| coughing up blood-stained phlegm (sputum) | 8(9) | 10(8) | 10(9) | n/a | 7(5) | 2(2) | 3(5) | n/a | 0(0) | 7(9) | 47(6) | 0.305 |
| chest or shoulder pain | 8(9) | 10(8) | 15(13) | n/a | 15(10) | 1(1) | 7(12) | n/a | 1(6) | 4(5) | 61(8) | 0.08 |
| other symptoms not listed above | 24(28) | 44(33) | 33(29) | n/a | 64(42) | 15(17) | 7(12) | n/a | 7(41) | 20(25) | 214(29) | <0.001 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| no symptoms | 5(6) | 6(5) | 6(5) | n/a | 2(1) | 31(36) | 12(20) | n/a | 0(0) | 10(12) | 72(10) | <0.001 |
| missing | 7(8) | 7(5) | 11(10) | n/a | 16(11) | 12(14) | 6(10) | n/a | 2(12) | 10(12) | 71(10) | 0.392 |
| **Cancer-specificity of symptom presented** | | | | | | | | | | | | |
| cancer-specific symptom | 62(73) | 97(73) | 79(69) | n/a | 94(62) | 36(42) | 38(62) | n/a | 10(59) | 48(59) | 464(64) | <0.001 |
| non-specific symptom | 11(13) | 23(17) | 19(17) | n/a | 39(26) | 7(8) | 5(8) | n/a | 5(29) | 13(16) | 122(17) | |
| no symptoms /missing | 12(14) | 13(10) | 17(15) | n/a | 18(12) | 43(50) | 18(30) | n/a | 2(12) | 20(25) | 143(19) | |

[1] Differences between jurisdictions (excluding Victoria and Norway) were tested by the Pearson's Chi[2] test, if nothing else stated.
[2] Differences between jurisdictions (excluding Victoria and Norway) were tested by the Fisher's exact test.

*Time intervals*

The observed time intervals are shown in Appendix C2 and are summarised in Figure 2. Based on overall trends, jurisdictions could be grouped into those with reduced, longer and similar intervals to Wales (Table 5). It was not possible to interpret variations observed in Norway (small sample size) and Victoria (surgical cohort). In the remaining jurisdictions, there was no difference in the median adjusted patient interval compared to Wales. Denmark had shorter median adjusted primary care interval (-11 days); Sweden had shorter (-20) and Manitoba longer (+40) diagnostic intervals compared to Wales. Denmark (-13), Manitoba (-11), England (-9) and Northern Ireland (-4) had shorter treatment intervals. The median adjusted total interval was shorter only in Denmark (Table 5, Figure 2). The differences were greater for the 90th percentile. The total interval in patients who waited longest (90th percentile) was significantly shorter in two jurisdictions (Denmark -142, England -28 days) compared to Wales.

**Table 5.** Differences in adjusted intervals (days) between Wales and the other nine jurisdictions for lung cancer patients

| Intervals | percentiles | Wales | Denmark | Sweden | England | N Ireland | Scotland | Manitoba | Ontario | Norway | Victoria |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Reference in days | Overall trend - shorter intervals | | | Similar with some intervals longer, some shorter | | Overall trend - longer intervals | | Difficult to interpret (see text for reasons) | |
| Ranking by 5-year survival rates for lung cancers diagnosed in 1999-2007 [5] | | 10 | 6 | 1 | 9 | 7 | 8 | 3 | 2 | 5 | 4 |
| Patient Interval | Number of patients | 181 | 233 | 172 | 213 | 179 | 169 | 133 | 205 | 55 | 141 |
| | 50th percentile (95% CI) | 21 | -6 (-13,0) | -1 (-9,8) | -3 (-10,5) | -3 (-13,6) | -3 (-10,4) | 1 (-8,10) | 1 (-11,14) | 0 (-8,8) | **-9** (-16,-2) |
| | 75th percentile (95% CI) | 61 | -13 (-38,13) | -2 (-24,21) | -2 (-42,37 ) | -8 (-55,39) | 1 (-25,27) | 3 (-23,30) | -7 (-54,39) | -9 (-60,42) | -4 (-46,38) |
| | 90th percentile (95% CI) | 216 | **-34** (-55,-13) | -1 (-25,23) | -15 (-42,12) | 24 (-21,70) | **43** (7,79) | **-35** (-59,-10) | **-34** (-66,-2) | **59** (21,96) | **-35** (-49,-21) |
| Primary Care interval | Number of patients | 110 | 159 | N/A | 147 | 124 | 119 | 80 | 75 | 19 | 89 |
| | 50th percentile (95% CI) | 20 | **-11** (-18,-3) | | -7 (-17,3) | -5 (-15,4) | -3 (-14,8) | 7 (-8,21) | 5 (-9,19) | **-11** (-18,-4) | -8 (-17,1) |
| | 75th percentile (95% CI) | 43 | **-29** (-47,-12) | N/A | -17 (-42,8) | 1 (-45,48) | -11 (-36,14) | 19 (-47,85) | 20 (-72,112) | -10 (-57,37) | -12 (-70,46) |
| | 90th percentile (95% CI) | 91 | -30 (-66,7) | | -39 (-85,6) | 17 (-55,90) | -20 (-67,25) | 13 (-38,65) | 102 (-56,258) | -22 (-109,66) | -19 (-89,51) |
| Diagnostic interval | Number of patients | 176 | 229 | 165 | 212 | 170 | 173 | 138 | 212 | 52 | 160 |
| | 50th percentile (95% CI) | 45 | -12 (-25,1) | **-20** (-35,-5) | 9 (-3,21) | 17 (-5,39) | -4 (-16,8) | **40** (14,66) | 10 (-6,26) | 4 (-16,24) | 7 (-13,27) |
| | 75th percentile (95% CI) | 108 | **-45** (-52,-39) | **-22** (-30,-15) | -7 (-20,7) | **12** (2,22) | -15 (-32,1) | **35** (22,48) | 5 (-9,19) | -4 (-15,8) | -2 (-8,4) |
| | 90th percentile (95% CI) | 162 | -27 (-153,99) | -34 (-206,138) | -14 (-100,72) | 112 (-165,389) | 31 (-81,143) | **112** (32,192) | 106 (-122,335) | 0 (-93,93) | **62** (10,114) |
| Treatment interval | Number of patients | 192 | 279 | 190 | 238 | 200 | 187 | 182 | 263 | 87 | 199 |
| | 50th percentile (95% CI) | 43 | **-13** (-15,-11) | -2 (-8,3) | **-9** (-12,-5) | **-4** (-7,-2) | 0 (-4,4) | **-11** (-17,-5) | 3 (-4,10) | **-8** (-11,-6) | **-29** (-32,-27) |
| | 75th percentile (95% CI) | 64 | **-32** (-36,-28) | -2 (-8,4) | **-18** (-23,-13) | **-13** (-18,-7) | 1 (-7,9) | -5 (-16,6) | 6 (-2,14) | **-13** (-19,-8) | **-33** (-41,-25) |
| | 90th percentile (95% CI) | 89 | **-45** (-50,-40) | **-10** (-17,-4) | **-28** (-36,-20) | **-16** (-23,-9) | -6 (-14,1) | 4 (-5,13) | 4 (-4,13) | **-22** (-30,-14) | **-39** (-45,-32) |
| Total | Number of patients | 147 | 192 | 147 | 176 | 153 | 143 | 117 | 178 | 52 | 113 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| interval | 50th percentile (95% CI) | 116 | **-49** (-95,-3) | -8 (-64,47) | -7 (-52,38) | -16 (-41,10) | -2 (-70,66) | 11 (-41,63) | 9 (-78,97) | **-34** (-56,-12) | -32 (-64,2) |
| | 75th percentile (95% CI) | 204 | -91 (-270,87) | -17 (-40,7) | -29 (-175,118) | 5 (-191,201) | 33 (-144,211) | 13 (-77,103) | -7 (-331,317) | -39 (-107,29) | -23 (-61,14) |
| | 90th percentile (95% CI) | 365 | **-142** (-150,-134) | -18 (-59,23) | **-28** (-37,-18) | 0 (-4,5) | 15 (-26,55) | 15 (-26,55) | 0 (-78,79) | **-84** (-119,-49) | 0 (-3,3) |

| **Interval relative to Wales** | **Trends** | **Significant** |
|---|---|---|
| Reduction | | |
| Increase | | |

The majority of patients were diagnosed between 2013-14. The differences were calculated for the 50th, 75th and 90th percentiles by setting age to its mean value and gender and comorbidity to their modes (i.e. male gender and medium comorbidity). It is not possible to interpret differences observed for Norway (due to the small sample size) and Victoria (the cohort was limited to those who had undergone surgery).

FIGURE 2

*Sensitivity and validity analyses*

The estimates of routes to diagnosis, time intervals, and regression analysis trends were not significantly altered by changing the cut-off to 6 months or using only patient data (results not shown).

Appendix C3 details, which sources were used based on the standardization rules, to define dates and also how often a day in the date was imputed. With regards to the dates of first presentation to healthcare (CCC=0.91), diagnosis (CCC ≥ 0.93) and treatment (CCC=0.94), there was adequate agreement between all data sources where the data on these dates was collected. Agreement between patient versus PCP for dates of first presentation to healthcare (CCC=0.91) and diagnosis (CCC=0.93) was also adequate as was agreement between patient versus CTS for dates of diagnosis (CCC=0.94) and treatment (CCC=0.94).

Omitting time intervals which were negative or over 365 days (Appendix C4) led to change in direction of difference which was non-significant in long intervals (75th or 90th percentile) between Wales and jurisdictions in four cases: Norway and Victoria (patient interval), N Ireland (diagnostic interval), England (total interval). All other results were similar to the main results.

## Discussion

*Main findings*

This is the first international study we are aware of comparing lung cancer routes and time intervals. With the exception of Denmark, in all other jurisdictions, the median total interval

from symptom onset to treatment, for respondents diagnosed in 2012-15 was similar to that of Wales, the reference. However, there were jurisdiction specific differences in patient, diagnostic and treatment intervals, especially for the 10% of patients who waited the longest. Based on overall trends, jurisdictions could be grouped into those with trends of reduced, longer and similar intervals to Wales.

Across jurisdictions, all symptoms other than persistent cough were less frequently reported by the PCP when compared to patients. This was especially true for fatigue and weight loss. One in four patients reported incidental diagnosis and one in ten were diagnosed following a visit to the emergency (A&E) department.

*Strengths and weaknesses*

Our study helps address the shortcomings of current international comparisons across multiple national studies with significant variation in methodology including differences in definition of intervals. Strengths of our study include 1) use of the same methodology across countries 2) use of cancer registries to identify consecutive newly diagnosed patients; 3) use of standardised questionnaires; 4) inclusion of PCP and CTS questionnaires enriched by registry data; 5) minimal data interpretation by the local teams with all data cleaning performed in a standardised manner centrally; and 6) triangulation with comprehensive data rules to ensure validity, consistency and preserve statistical precision.[21] Recall bias was minimised by the triangulation of different data sources and by patients completing the questionnaire within a limited time window (median 5 months) after the cancer diagnosis.

A key limitation, as with all questionnaire-based studies was both selection and non-response bias which varied across jurisdictions and has implications for interpretation and generalisation of findings [34]. In comparing intervals, we adjusted for age, sex and comorbidity but were unable to adjust for ethnicity and education due to different classification systems. Recall bias was minimised by the triangulation of different data sources and by patients completing the questionnaire within a limited time window (median 5 months) after the cancer diagnosis. Recruitment of patients up to 9 rather than 6 months after diagnosis might have magnified the selection bias due to high mortality.[35] However, sensitivity analysis suggests that this did not impact on the results. Categorising presenting symptoms into indicative or not was done pragmatically as existing guidelines for lung cancer investigation vary across ICBP jurisdictions.[36] In Norway and Victoria, a small sample size and restriction of eligibility to only surgical patients, respectively, made comparison difficult. Nonetheless, significant differences in these two jurisdictions compared to Wales were largely limited to the treatment interval alone.

There was variation in stage distribution across jurisdictions. While this may be partly related to the varying response rate, true differences in lung cancer stage have been noted on analysis of registry data of patients diagnosed between 2004-2007.[6] The high lung cancer mortality and self-selection are likely to have contributed to an over-representation of early stage disease and tumours treated with surgical resection. This suggests that true variation may well be higher than that reported in this cohort of 'healthier early stage' patients.

*Comparison to other studies*

The most common patient-reported symptoms, in keeping with the literature, were persistent cough, breathlessness, fatigue and weight loss, with one in five reporting 'no symptoms'.[18] Only a minority (11%) of our respondents reported coughing blood or bloody sputum/spit, which is the only consistent predictor of lung cancer.[37] While haemoptysis was reported in a prospective survey (England 2011-12) by 22% of lung cancer patients identified through respiratory clinics, it was a presenting symptom in only 5% of cases.[11]

The median number of symptoms reported by patients was more than that reported by the PCP in all jurisdictions. This was especially so for fatigue and weight loss. A number of factors could have contributed to this - patients not listing all symptoms at presentation, patients having a different understanding/recall of their symptoms post diagnosis, PCPs only recording key symptoms such as cough. Further research on under reporting of systemic symptoms such as fatigue and weight loss is warranted.

As lung cancer mortality is higher in patients attending emergency (A&E) departments, the rates are often compared in an attempt to understand international survival differences.[38] The rate of respondents who attended A&E varied two-fold across jurisdictions from 9-10% in England, Scotland and Denmark to 18-20% in Northern Ireland, Ontario and Manitoba. While rates for Scotland (10%) were similar to that reported in a prospective Scottish audit (11.5%), as were rates for Denmark (7% vs 6.3% when PCP not involved), rates for England (9%) were lower than those reported in population based audits (25%) reflecting non-response bias.[14,15] In Victoria (4%) restriction of the cohort to surgical patients is likely to have accounted for the very low rates.

Our reported median patient, primary care and diagnostic intervals are in keeping with those previously reported from the participating jurisdictions (Table 6). Minor variations in interval estimates are likely due to differences in data source, sample size and cohort characteristics.[39] Longer intervals were reported from earlier cancer cohorts - median

primary care interval for England of 52 days in 1998-2000 (our median 11),[13] median total interval for Denmark of 108 days in 2004-5 (our median 67) and Norway of 118 in 2002-5 (our median 79).[17-19,24]

**Table 6.** Summary of literature on intervals in lung cancer patients diagnosed since 2000 in the ICBP Module 4 countries

| Study No | Ref | Study Period | Jurisdiction | Design | Patients | No. of lung cancer patients | Interval[1] (days) | | | | Total interval |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Patient | Primary care | Diagnostic | Treatment | |
| 1 | Walter FM et al (2015) | 2011-2 | England, UK | Prospective patient questionnaire survey - multi hospital cohort. Dates of diagnosis based on medical note review. | All attending urgent and routine respiratory clinics across the five hospitals in England aged over 40 years with symptoms suspicious of lung cancer. | 153 | Interval from first symptom to diagnosis Median 91 (IQR 49-184) | | | | |
| 2 | Lyratzopoulos G et al (2015) | 2009-10 | England, UK | Prospective national audit of cancer diagnosis using primary practice patient records and continuous sampling during audit period | All patients aged ≥15 years who had first presented to a primary care practitioner and were subsequently diagnosed with one of 28 cancers | 1128 | Median 11 (IQR 0-32) | Median 3 (IQR 14-39) | | | |
| 3 | Neal R et al (2014) | 2007–8 | UK | Retrospective analysis of electonic health record data from General Practice Research Database - population cohort | All newly diagnosed with one of 15 cancers | 2851 | | | Median 112 (IQR 45-251) | | |
| 4 | Barrett J et al (2008) | 1998-2002 | Exeter, England, UK | Retrospective case-control review of PCP records - population cohort | All with lung cancer aged ≥ 40 years, identified from the hospital cancer registry and computerised searches of all primary care practices | 247 | | Median 52 (IQR 7–243) | | | |
| | | | | | | | Interval from first symptom to diagnosis - Median 121 (IQR 53,261) | | | | |
| 5 | Baughan P et al (2009) | 2005-6, 2007-8 | Scotland, UK | Retrospective audit involving PCP review of medical records of all newly diagnosed cancer patients they had seen - population cohort | All newly diagnosed with lung cancer | 981 | Median 9.5 (IQR 31) | | Median 11 (IQR 28) | | |
| 6 | Guldbrandt LM et al (2015) | 2010 | Denmark | Retrospective PCP questionnaires survery of national registry-based population cohort | All consecutive newly diagnosed lung cancer patients | 429-442 depending on interval | | Median 7 (IQR, 0-30) | Median 29 (IQR, 12-69) | | |
| 7 | Tørring ML et al (2013) | 2004 - 5 | Aarhus, Denmark | Prospective, population-based study using electronic health records and PCP survey of identified patients | All newly diagnosed with lung cancer after attending primary care | 262 | | | Median 112 (IQR 45-251) | | |
| 8 | Hansen RP et al (2011) | 2004-5 | Aarhus, Denmark | Retrospective PCP survey | Cancer patients newly diagnosed during a 1-year period identified using administrative registry data | 128-251 (depending on interval) | Median 28 (IQR 7-56) | Median 0 (IQR 0-9) | | Median 51 (IQR 27-76) | Median 108 (IQR 82-167) |
| 9 | Bjerager M et al (2006) | 2003 | Aarhus, Denmark | Retrospective PCP survey using structured telephone interviews enriched with administrative registry data - population-based cohort | All lung cancer patients identified through histological and cytological tests from county-based registers | 84 | | Median 32.5 (IQR 12–68) | | | |
| 10 | Rolke HB et al (2006) | 2002-5 | Norway (South) | Retrospective questionnaire-based patient survey - hospital cohort | All newly diagnosed with lung cancer | 273 -376 (depending on interval) | Median 19 (2–77) | | | | Median 118 (IQR 68–220) |
| 11 | Stokstad T et al (2017) | 2011-13 | Norway | Retrospective medical record audit -single hospital cohort | All cases that started diagnostic work-up and were diagnosed with lung cancer at St. Olavs Hospital, Trondheim | 449 | | | | 42 days (range: 2–296) | |
| 12 | Largey G et al (2016) | 2013 | Victoria, Australia | Retrospective medical record audit -three hospital cohort | Admitted with a new diagnosis of lung cancer over a three month period in three hospitals | 78 | | | | Mean 30.4 (SD 45.3) | |
| 13 | Evans SM et al (2016) | 2011-4 | Victoria, Australia | Retrospective medical record audit - multi hospital cohort | All lung cancer patients newly diagnosed in six public and two private hospitals | 1417 | | | Median 15 (IQR, 5–36) | Median 30 (IQR, 6–84) | |
| 14 | Emery JD et al (2017) | 2012 -4 | Western rural Australia | Prospective cluster randomised trial of symptom awareness | Lung cancer patients newly diagnosed in the control arm of the trial | 167 | Interval from first symptom to diagnosis Median 34.5 (IQR 7 103.5) | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 15 | Burneister BH et al (2010) | 2000-4 | Queensland Australia | Retrospective analysis of radiation therapy waiting times | All lung cancer patients who received radiation therapy as initial treatment at a public hospital. | 1535 | | | | | Median 33[2] |
| 16 | Ellis PM and Vandermeer R (2011) | 2010 | Ontario, Canada | Retrospective patient survey using structured telephone interviews - single centre cohort. Appointment dates and diagnostic tests verified through family doctor or patient chart review. | All lung cancer patients referred to a regional cancer centre | 52 | | Median 21 | Median 27 (IQR 0-38) | | Median 138 (IQR 79-175) |
| 17 | Lo DS et al (2007) | 2005-7 | Ontario, Canada | Retrospective medical record audit - multi hospital cohort | All with lung cancer seen on a newly implemented Time to Treat Program | 144 | | | Median interval from suspicion of lung cancer to diagnosis 37 | | |

[1] Intervals as defined in Figure 1; [2] Limited to patients receiving radiation treatment

Across all jurisdictions, there was no significant difference in primary care intervals for the 10% of patients with longest interval. It is likely that these patients had vague or non-specific symptoms and signs. Referral guidelines for suspected lung cancer do not always favour patients with early symptoms and often prioritise those with more advanced disease.[40] Access to better diagnostic tools such as low-dose CT chest in the primary care setting may favour this group of patients.[41] It would be useful in future projects to explore whether such access may have contributed to the improved 1-year lung cancer survival rates reported from Australia and Canada.[6]

Diagnostic intervals were significantly longer for Manitoba compared to other jurisdictions and twice that reported in an ongoing local PCP audit (personal communication). While one might suspect overestimation due to differences in the source of date of first presentation, between our study (in almost half, it was derived from patients) and local audit, this is less likely as the concordance coefficient between PCP and patient derived data at Manitoba was 0.94.

Observed median treatment intervals were below 6 weeks for nearly all jurisdictions. This was the only interval where there were significant differences between jurisdictions with Denmark, England, Norway and Northern Ireland all having shorter adjusted treatment intervals across all percentiles, with larger differences for the 75$^{th}$ and 90$^{th}$ percentile. These improvements may reflect implementation of waiting time targets in Denmark (35-38 days from first consultation depending on treatment modality) and the UK (31 days from decision to treat).[42,43] The shorter treatment intervals in Norway are in keeping with long-standing provision of standardized cancer care pathways and effective coordination between primary care and treatment centers. While a systematic review did not find evidence to support an association between intervals and lung cancer outcomes, increasing mortality with longer diagnostic intervals was noted in a more recent, high-quality study.[16] In 2000, O'Rourke reported median intervals of 94 days (35-187) between the first hospital visit and starting treatment resulting in 21% of potentially curable patients becoming incurable.[44] Others have found metabolic evidence on PET/CT of pre-treatment disease progression in 21% and TNM upstaging in 18% of small-cell lung cancer patients after a relatively short median inter-scan interval of 43 days.[45] Long intervals can also result in deterioration in performance status. More recently, there is concern that the need for genotyping may result in further increase in time to treatment.

The shorter total interval in Denmark likely reflects the significant reductions in cancer waiting times following a collaborative effort to set-up and implement a national centralised quality

management system, the Danish Cancer Patient Pathways (CPPs). The latter includes PCP access to fast-track diagnostic work-up.[46]. The findings are in keeping with higher relative survival and lower mortality in Denmark among symptomatic cancer patients diagnosed through primary care after the implementation of CPPs and with the accelerated increase in 5-year survival among Danish lung cancer patients diagnosed in 2010-2014 when compared to patients from earlier time periods.[47] While there is some inherent lead-time bias, the findings highlight the importance and feasibility of a timely diagnosis of lung cancer.

*Conclusions*

The study provides for the first time, comparable data, collected through consistent methods in all jurisdictions, allowing for detailed comparisons of key diagnostic intervals in lung cancer and routes to diagnosis. While all jurisdictions except Denmark, had similar median adjusted total intervals, there were jurisdiction-specific significant differences in patient, diagnostic and treatment intervals, especially for the 10% of patients who waited the longest. The proportion of patients diagnosed following presentation to the PCP ranged from 35-75%. These data could help individual jurisdictions to better target their efforts to reduce time to treatment and ultimately improve patient experience and outcomes in lung cancer.'

Intervals and pathways are ultimately of interest as they relate to prognosis. A further analysis which includes all four cancers (lung, ovary, colon and breast) surveyed in ICBP4 module and explores the impact of these intervals on stage and 1-year survival is underway.

**List of abbreviations**

ICBP M4 – International Cancer Benchmarking Partnership Module 4
PCP – Primary Care Physician
CTS – Cancer Treatment Specialist
CPP – Danish Cancer Patient Pathways

**Figure headings**

Figure 1: Time intervals from onset of symptoms to start of treatment based on the Aarhus Statement

Figure 2: Differences in 50th, 75th and 90th centiles of the intervals (days) between Wales as the reference and the other nine jurisdictions. The data are adjusted for differences in age, gender and comorbidity. The bars in black show significant differences in intervals.

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UM, DW, PV, AZF, HJ planned the study design, data collection, carried out the analyses and wrote the draft manuscript. UM, PV, DW, HJ, AB, AKK, RJB, DHB, JK, VC, ATG, EG, EH, ML, RJW, YL, MM, DT, RDN, VW, IR and SH were responsible for local data collection (alongside the Working Group), management and interpretation, and have participated in writing and have approving the final manuscript version. JB, OB and OTB provided advice on the interpretation of results in their respective jurisdictions and comments or substantial edits on the manuscript, approving the final version.

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None

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**Availability of data and material**

The data that support the findings of this study are available from the named authors from each ICBP jurisdiction, but restrictions apply to the availability of these data and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the ICBP Programme Board. Please contact the ICBP Programme Management team, based at Cancer Research UK, with any queries (icbp@cancer.org.uk).

**Ethics approval and consent to participate**

For each local data collection, there were specific procedures and approvals which included anonymised data transfer to University College London and Aarhus University. Approvals were received from the following institutions: Cancer Council Victoria Human Research Ethics Committee [HREC 1125]; Health Research Ethics Board, University of Manitoba [HS15227 (H2012:105)]; Research Resource Ethics Committee, CancerCare Manitoba [RRIC#28-2012];

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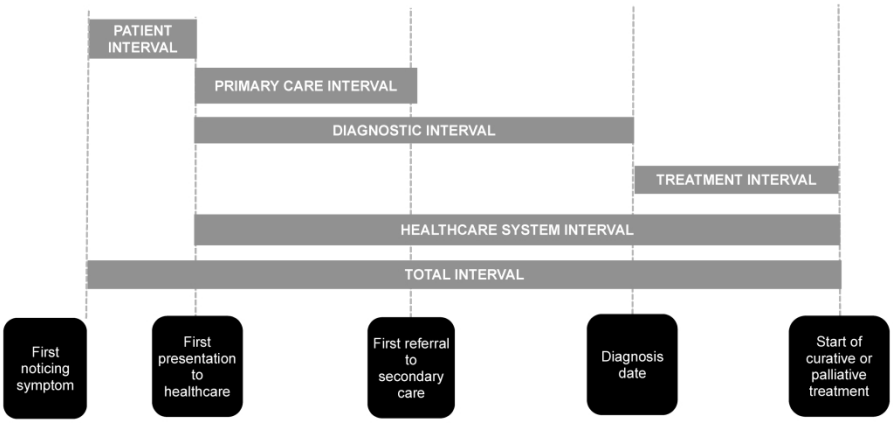
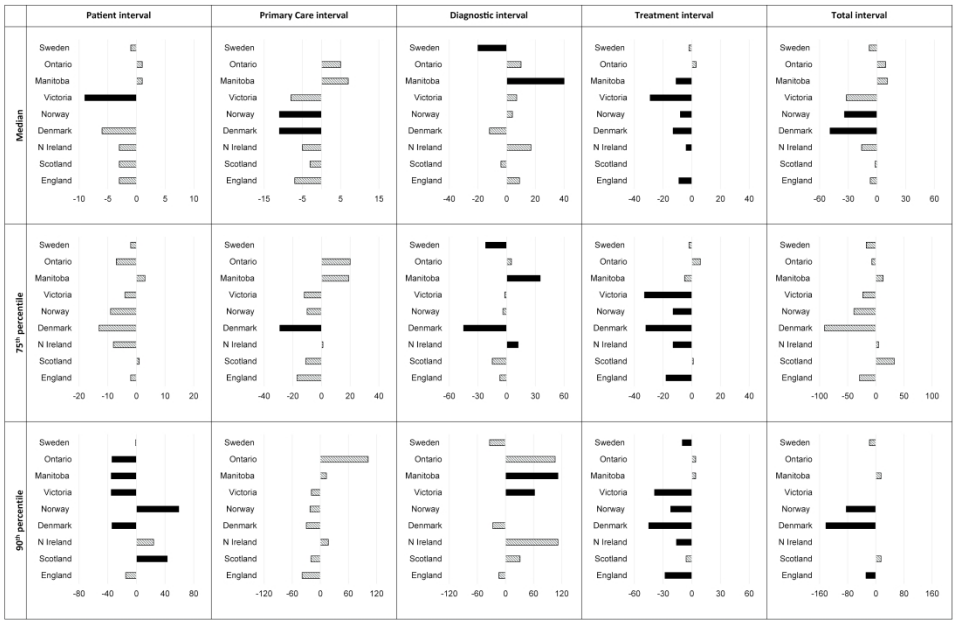



Time intervals from onset of symptoms to start of treatment based on the Aarhus Statement




Differences in 50th, 75th and 90th centiles of the intervals (days) between Wales as the reference and the other nine jurisdictions. The data are adjusted for differences in age, gender and comorbidity. The bars in black show significant differences in intervals.

420x297mm (300 x 300 DPI)

# Supplementary Web Appendix

## Contents

## Appendix A: Lung cancer questionnaires

A1: Patient questionnaire

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# International Cancer Benchmarking Partnership Module 4

## Patient questionnaire

## Lung Cancer

Thank you very much for taking the time to fill in this questionnaire – it should take about 20 minutes to complete. We are sending the questionnaire to a large sample of people who we understand have had a diagnosis of lung cancer. If this has been sent to you in error and you do not have cancer, please do not continue and return the documents in the prepaid envelope.



Our aim is to gain a better understanding of the process by which people have their cancer diagnosed. We would also like to find out more about the symptoms they experience (if any), and the pathway they follow from start of symptoms to treatment of their cancer. This will help in identifying ways in which cancers can be diagnosed quickly and effectively. Thank you once again for your time.

**This information is confidential and will not be passed to anyone involved in your treatment.**

Name: _____

Date of Birth: _____

Address: _____

_____

_____

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## Consent form

Please read the consent form and sign your name and date **BELOW**.

If you require any clarification, please do not hesitate to ring the study team members. Their contact details are found on the information sheet.

**Please be reassured that your responses are completely confidential and will not be passed to anyone involved in your treatment. For the purposes of the study it is important that you agree to consent to all the statements listed below.**

- I confirm that I have read the attached information sheet and I understand why the research is being done.
- I am willing for the team to request information from my GP and hospital doctors which is relevant to the audit as described in the information sheet.
- I give permission for my details (name, address) to be given to the cancer registry (NHS Information Centre for Health and Social Care) for follow up.
- I agree for the information I have provided and any other relevant information from my medical records to be stored as described in the information sheet under the custodianship of University College London.
- I consent to sharing of coded data which contains no personal identifiers between researchers, some of whom are located outside the European Union.
- I consent for use of my data if I become mentally incapacitated during the course of the project.

**I agree to all the statements listed and consent to participate in the study.**

Name (Please print) _____

Signature: _____ Date: _____

If we have any questions, may we phone you for clarification?
(Please tick) ☐ **Yes** ☐ **No**

If **Yes**, please provide your telephone number: _____

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**1. Please can you confirm the details of your GP/GP practice (name, practice address – as best as you can remember): We appreciate that you may have more than one GP involved in your care – in which case, we are interested in the GP you would say provides the majority of your care, particularly relating to the cancer you've had diagnosed.**

Name of doctor

Name of practice

Address

Postcode

Town

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**2. Which of the following best describes the events which led to your diagnosis of cancer?** (please tick only **ONE** answer)

| | ✓ |
|---|---|
| I had symptoms/I noticed a bodily change and went to see a doctor (e.g. GP) | |
| I had symptoms/I noticed a bodily change and went/was taken to Accident and Emergency (A&E) | |
| I had seen a doctor/GP with symptoms, but went/was taken to Accident and Emergency (A&E) when things worsened | |
| I was being investigated by my doctor(s) for another problem during which time the cancer was discovered | |
| Other (please describe): | |

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**3. The following health concerns or symptoms are commonly experienced with lung cancer.**

| |
|---|
| Cough |
| Breathlessness |
| Being short of breath |
| Chest pain / Pain on breathing |
| Coughing up blood |
| Bloody sputum/blood in spit |
| Unexplained weight loss |
| Loss of appetite |
| Fatigue |



**Please write down ALL health concern(s) or symptom(s) you may have had before contacting a doctor or taking part in screening. It does not matter if they are not included in the list above:**

| Please write your health concern(s) or symptom(s) in the boxes below: |
|---|
| 1) |
| 2) |
| 3) |
| 4) |
| 5) |
| 6) |

| | |
|---|---|
| This is not applicable to me (e.g. I did not have any symptoms), please tick | ✓ |

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**4. Please write down your best estimate of the date you noticed the first of these health concern(s) or symptom(s).** If you cannot remember the exact date, you can fill in the month and the year.

Day (optional), month, year

| D | D | M | M | Y | Y | Y | Y |
|---|---|---|---|---|---|---|---|
| | | | | | | | |

| | ✓ |
|---|---|
| This is not applicable to me (e.g. I had no symptoms), please tick | |

**5. Approximately how long did you have health concern(s) or symptom(s) before contacting a doctor? (Please think of the first visit to the doctor, not re-visits after that).** Please tick only **ONE** answer.

| | ✓ |
|---|---|
| Less than 1 week | |
| 1-2 weeks | |
| 3-4 weeks | |
| 5-7 weeks | |
| 2-5 months | |
| 6-12 months | |
| More than 12 months | |

| | ✓ |
|---|---|
| This is not applicable to me (e.g. I had no symptoms), please tick | |

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**6a. Once you contacted a practice about your health concern(s) or symptom(s), how long did it take to get an appointment with a doctor? (Please think of the first visit to the doctor, to discuss your health concern(s) or symptom(s)).**
Please tick only **ONE** answer.

| | ✓ |
|---|---|
| Same day/next day | |
| Within 1 week | |
| 1-2 weeks | |
| 3-4 weeks | |
| Longer | |
| If there was no waiting time (e.g. you went/were taken to A&E), please tick this box | |
| This is not applicable to me (e.g. I had no symptoms), please tick | |



**6b. What was the date you first saw your doctor about your health concern(s) or symptom(s)?** If you cannot remember the exact date, you can fill in the month and the year.

Day (optional), month, year

| D | D | M | M | Y | Y | Y | Y |
|---|---|---|---|---|---|---|---|

| | ✓ |
|---|---|
| This is not applicable to me (e.g. I had no symptoms), please tick | |

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**7. How many times did you visit the following for the investigation of your symptoms before your cancer was diagnosed?**

| | Please write down the number of visits |
|---|---|
| GP | |
| Hospital | |
| Consultant/specialist outside of a hospital | |

✓

| | |
|---|---|
| This is not applicable to me (e.g. I had no symptoms), please tick | |

**8a. After your doctor referred you to a specialist, how long did it take you to get an appointment?** Please tick only **ONE** answer.

✓

| | |
|---|---|
| Less than 1 week | |
| 1-2 weeks | |
| 3-4 weeks | |
| 5-7 weeks | |
| 2-5 months | |
| 6-12 months | |
| More than 12 months | |

✓

| | |
|---|---|
| This is not applicable to me (e.g. my doctor did not refer me), please tick | |

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**8b. What was the date of your first appointment with a doctor, involved in investigating and/or treating your cancer, to whom you were referred?**
If you cannot remember the exact date, you can fill in the month and the year.

Day (optional), month, year

| D | D | M | M | Y | Y | Y | Y |
|---|---|---|---|---|---|---|---|

| This is not applicable to me (e.g. my doctor did not refer me), please tick | ✓ |
|---|---|

**9. What was the date you were told you had cancer?** If you cannot remember the exact date, you can fill in the month and the year.

Day (optional), month, year

| D | D | M | M | Y | Y | Y | Y |
|---|---|---|---|---|---|---|---|

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**10. Have you had any of the following treatments for your cancer yet? If so, please can you estimate the date this treatment started?** Please tick **ALL** that apply. If you cannot remember the exact date, you can fill in the month and the year.

| | Type of treatment | | Date of treatment (give first date if you had more than one) |
|---|---|---|---|
| a. | Surgery | ☐ Yes ☐ No | Day (optional), month, year D D M M Y Y Y Y |
| b. | Chemotherapy | ☐ Yes ☐ No | Day (optional), month, year D D M M Y Y Y Y |
| c. | Radiotherapy | ☐ Yes ☐ No | Day (optional), month, year D D M M Y Y Y Y |
| d. | Other Please specify: | ☐ Yes ☐ No | Day (optional), month, year D D M M Y Y Y Y |
| e. | Treatment not started yet | ☐ Yes | |

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**11. Who is the consultant doctor who has taken responsibility for diagnosing and or/treating your cancer?**

| |
|---|
| Name of consultant: |
| Hospital name: |
| Hospital department: |

**Please can you answer some more general questions about your health?**
It will help us in interpreting your responses to this questionnaire to know about your general health and other health problems you may have had in the past.

**12. Looking back to the 2 years before you were diagnosed with cancer, would you say your general health was** (Please tick only **ONE** answer.)**:**



| | ✓ |
|---|---|
| Very good | |
| Good | |
| Fair | |
| Poor | |
| Very poor | |

**13. Have you been treated before for any of the conditions below?**
Please tick 'yes' or 'no' for each condition:

| | | |
|---|---|---|
| Heart disease | ☐ **Yes** | ☐ **No** |
| Stroke | ☐ **Yes** | ☐ **No** |
| Lung disease (excluding lung cancer) | ☐ **Yes** | ☐ **No** |
| Diabetes | ☐ **Yes** | ☐ **No** |

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**Finally, a little more information about you.** The information you provide below will help us to analyse the results of the survey in more detail.

**14. Which of these best describes your ethnic group? (please tick one box, as appropriate).** If you are descended from more than one ethnic or racial group, please tick the group you consider you belong to, or tick 'any other ethnic group'.

| | ✓ | | ✓ | | ✓ | | ✓ |
|---|---|---|---|---|---|---|---|
| White | | Chinese | | Black - Caribbean | | Black - African | |
| Black - other | | Indian | | Pakistani | | Bangladeshi | |
| Any other ethnic group, please specify: | | | | | | | |



**15. What is the main language spoken in your home?** Please tick

| | ✓ |
|---|---|
| English | |
| Other, please specify: | |

**16. What is the highest level of education you have achieved?**
Please tick only **ONE** answer.

| | ✓ |
|---|---|
| Finished school at or before the age of fifteen | |
| Completed GCSEs, O-levels or equivalent | |
| Completed A Levels or equivalent | |
| Completed further education but not a degree | |
| Completed a Bachelor's degree / Masters degree / PhD | |
| Other, please specify: | |

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**17. Have you ever smoked cigarettes, including hand-rolled ones, pipes or cigars?**

☐ Yes ☐ No

**18. Are you a current smoker, smoking either cigarettes, including hand-rolled ones, pipes or cigars?**

☐ Yes ☐ No

**19. If you are a current smoker or have smoked in the past, how many cigarettes, including hand-rolled ones, pipes or cigars on average do you smoke/have you smoked per day?**

| Number per day: | |
|---|---|

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## 20. Further comments

**Please add anything else that you would like to tell us about your cancer diagnosis or treatment.**



**Thank you very much for taking the time to complete this questionnaire.**

A2: Primary care physician (PCP) questionnaire

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# International Cancer Benchmarking Partnership Module 4

## Primary Care Audit

## Lung Cancer

Thank you very much for agreeing to fill in this questionnaire. As part of an international study examining differences in cancer survival, we are sending the questionnaire to health care providers of a sample of consented patients with cancer.

Our aim is to gain a better understanding of the process by which people have their cancer diagnosed – the symptoms they experience, and the pathway they follow from onset of symptoms to treatment of their cancer. This will help in identifying ways in which cancers can be diagnosed and treated quickly and effectively. Thank you once again for your time.



**Please can you refer to your patient's notes in completing the questionnaire as this will help in obtaining accurate data on time points.**

If you would prefer to return this questionnaire without the patient details, please tear off along the dotted line

ID-number: Jurisdiction-ID + Patient-ID:

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**Patient information**

ID-number: Jurisdiction-ID + Patient-ID:

Full name:

Address:

Postcode:

Date of birth: D D M M Y Y Y Y

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## 1. Duration of symptoms

Please estimate how long your patient had symptom(s), attributable to lung cancer, before attending your practice (or other health service).

We appreciate that identifying a 'date of first symptom' is not always straightforward – particularly when there are multiple and/or chronic symptoms. Nevertheless, we hope you can provide a 'best estimate'.

| **Estimate of symptom duration** (please tick **one**): | ✓ | **What were the symptoms?** Please describe: |
|---|---|---|
| Less than 1 week | | |
| 1 to 4 weeks | | |
| 5 to 7 weeks | | |
| 2-5 months | | |
| 6-12 months | | |
| More than 12 months | | |
| Not possible to estimate | | |
| No symptoms (e.g. screen detected cancers) | | |

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## 2. Pathway of presentation

### 2.1 Through what route did the patient first present? Please tick **ONE**:

| | ✓ | |
|---|---|---|
| Your patient first presented to primary care (either in-hours or out-of-hours) | | Please can you provide your best approximation of the date of this **primary care** visit<br>D D M M Y Y Y Y |
| Your patient presented straight to A&E (with or without your involvement) | | |
| Your patient first presented to primary care, but then at a later date presented to A&E as an emergency (with or without your involvement) | | Please can you provide your best approximation of the date of this **primary care** visit<br>D D M M Y Y Y Y |
| Other – please describe: | | |

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**3. Date you ordered any tests/investigations in response to symptom(s).**

We are interested in any kind of tests/investigations (e.g. imaging etc) that you may have ordered. Please only consider the tests/investigations that you ordered yourself. Please tick **all** that apply and put in the date that the test/investigation was ordered:

| | ✓ | |
|---|---|---|
| Chest x-ray | | D D M M Y Y Y Y |
| MRI scan | | D D M M Y Y Y Y |
| CT scan | | D D M M Y Y Y Y |
| PET scan | | D D M M Y Y Y Y |
| Sputum test | | D D M M Y Y Y Y |
| Lung biopsy | | D D M M Y Y Y Y |
| Bronchoscopy | | D D M M Y Y Y Y |
| Other (please specify): | | D D M M Y Y Y Y |



**4. Date of referral to specialist medical services**

At what date did you **first** refer the patient to hospital or another specialist transferring the responsibility for on-going investigation/treatment to other medical services?

D D M M Y Y Y Y

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## 5. Nature of this referral

**5.1 Do you know the date that the patient was seen for this referral?**

☐ **Yes**, please provide the date: D D M M Y Y Y Y

☐ **No**

**5.2 If you did make a referral to specialist services, which of the following best describes the nature/characteristics of this referral?** Please tick **one**.

| | ✓ |
|---|---|
| Emergency admission: a referral to A&E (or equivalent) for immediate admission | |
| An urgent referral for assessment of cancer symptoms/signs/test results (Note this will be within 2 weeks for England/Wales) | |
| A less urgent referral in which cancer is raised as a possibility (Note this will be greater than 2 weeks for England/Wales) | |
| A more general referral for investigation and assessment without cancer mentioned | |
| No referral was made | |
| Other – please describe | |



**5.3 Would you say this patient's diagnostic pathway was conducted predominantly in the public or private system?** Please tick **one**.

| | ✓ |
|---|---|
| Public healthcare system | |
| Private healthcare system | |

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## 6. Date of lung cancer diagnosis

This can be decided in different ways. Please tick **all** that apply.
Please provide whichever of the following dates you have to hand:

| | ✓ | |
|---|---|---|
| Date of histological confirmation [ideal] | | D D M M Y Y Y Y |
| Date results of investigation (histological or other) confirming cancer received | | D D M M Y Y Y Y |
| Date patient was told | | D D M M Y Y Y Y |
| Date biopsy undertaken | | D D M M Y Y Y Y |
| Date patient was first admitted to hospital because of the malignancy | | D D M M Y Y Y Y |
| Other (please specify) | | D D M M Y Y Y Y |

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## 7. Additional information

Finally, we are interested to know what other conditions your patient has, and the severity/impact of these conditions

Have you and/or any of your partners treated this patient (or has the patient been to hospital) for any of the following conditions? Please tick **all** that apply:

| | |
|---|---|
| Cardiovascular disease | ☐ Yes ☐ No |
| Stroke | ☐ Yes ☐ No |
| Lung disease (except lung cancer) | ☐ Yes ☐ No |
| Diabetes | ☐ Yes ☐ No |



**Are there any other comments you would like to make about this patient?**

Name (and title): _____

Signature: _____

Date: _____

**Thank you very much for taking the time to complete this questionnaire.**

A3: Cancer treatment specialists (CTS) questionnaire

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# International Cancer Benchmarking Partnership Module 4

## Specialist Care Audit

## Lung Cancer

Thank you very much for agreeing to fill in this questionnaire – it should take about 10 minutes to complete. As part of an international study examining differences in cancer survival, we are sending the questionnaire to health care providers of a sample of patients with cancer.

Our aim is to gain a better understanding of the process by which people have their cancer diagnosed – the symptoms they experience, and the pathway they follow from onset of symptoms to treatment of their cancer. We hope you can help us with information on this patient's cancer journey once they were referred to specialist cancer services. This will help in identifying ways in which cancers can be diagnosed and treated quickly and effectively.



**Thank you once again for your time**

**Please can you refer to your patient's notes in completing the questionnaire, as this will help in obtaining accurate data on time points.**

If you would prefer to return this questionnaire without the patient details, please tear off along the dotted line.

Your patient _____

is participating in the study.

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**Patient information**

ID-number: Jurisdiction-ID + Patient-ID:

Full name:

Address:

Postcode:

Date of birth: D D M M Y Y Y Y

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1. **Date patient first attended hospital/specialist services related to their cancer diagnosis.** We appreciate this date can at times be difficult to identify, particularly when there have been multiple visits in the lead up to a definitive diagnosis. Put another way, it's the date that the hospital/specialist service assumed responsibility for on-going investigation/treatment for your patient.

Day (optional), month, year

| D | D | M | M | Y | Y | Y | Y |
|---|---|---|---|---|---|---|---|
| | | | | | | | |

2. **How was the patient referred to the hospital/specialist services related to their cancer diagnosis?** Please tick.

Was it through a:

| | ✓ | | ✓ |
|---|---|---|---|
| GP referral | | Referral from respiratory clinic | |
| Medical specialist/Consultant referral | | Other referral – please specify: | |



3. **Where did this first contact/appointment happen?** Please tick.
Which of the following best describes where this first contact/appointment took place?

| | ✓ | | ✓ |
|---|---|---|---|
| Emergency department ('A&E') | | Medical outpatient department, please specify which department | |
| Oncology general outpatient department | | Surgical outpatient department, please specify which department | |
| Other – please specify: | | | |

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## 4. Date of diagnosis

This can be decided in different ways.
Please tick and complete as many of the following dates as possible.

| | ✓ | |
|---|---|---|
| Date of histological confirmation (ideal) | | Day (optional), month, year D D M M Y Y Y Y |
| Date results of investigation confirming cancer received | | Day (optional), month, year D D M M Y Y Y Y |
| Date patient was told | | Day (optional), month, year D D M M Y Y Y Y |
| Date of biopsy | | Day (optional), month, year D D M M Y Y Y Y |
| Date patient was first admitted to hospital because of the malignancy | | Day (optional), month, year D D M M Y Y Y Y |
| Date of MDT confirmation of diagnosis | | Day (optional), month, year D D M M Y Y Y Y |
| Other (please specify): | | Day (optional), month, year D D M M Y Y Y Y |

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## 5. Date treatment for the cancer commenced

Based on your records, when would you say that any treatment specifically targeting the patient's cancer started?

Day (optional), month, year

| D | D | M | M | Y | Y | Y | Y |
|---|---|---|---|---|---|---|---|

## 6. Additional information

Please can you provide any further information on the patient's cancer:

| **TNM**, please tick as appropriate: | |
|---|---|
| 0 | |
| I | |
| IIA | |
| IIB | |
| IIC | |
| IIIA | |
| IIIB | |
| IIIC | |
| IV | |
| Not able to stage | |

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**6.1 Histological subtype:** ✓

| | |
|---|---|
| Squamous cell carcinoma | |
| Adenocarcinoma | |
| Large cell carcinoma | |
| Non-small carcinoma | |
| Small cell carcinoma | |
| Carcinoid | |
| Unclassified | |
| Other (please specify): | |

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## Further comments

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Name (and title):

Signature:

Date:



Are you a ... (please tick below):

| | ✓ |
|---|---|
| Surgeon | |
| Medical Oncologist | |
| Clinical Oncologist | |
| Clinical Nurse Specialist | |
| Other (please specify): | |

**Thank you very much for taking the time to complete this questionnaire.**

## Appendix B:

## Rules for missing, incomplete, multiple response and out of range data

| |
|---|
| 1. Oversampling<br>To handle oversampling in Ontario, include only the first 315 consecutive lung cancer patients; |
| 2. Language/Participation in study/Presence of cancer<br>Exclude patients who checked "No, I don't understand the language" or "I don't want to participate in this study" or "I don't have cancer". |
| 3. Survey responders<br>a) Exclude Patient/PCP/Specialist survey from the analysis, if it was not written by Patient/PCP/Specialist (example: a medical oncologist completed a PCP survey);<br>b) In the case of duplicates, include only the first survey (example: 2 specialists completed surveys for the same patient). |
| 4. Gender<br>Exclude patients with unknown Gender. |
| 5. Age<br>a) Exclude patients with unknown age;<br>b) Exclude patients younger 40 years;<br>c) Use registry data, if Age is reported by both patient and registry. |
| 6. No cancer or Previous cancer in the same organ<br>a) Exclude patients with no cancer based on registry data;<br>b) Exclude patients with previous cancer in the same organ based on data from registry or free-text for Presentation in the patient survey. |
| 7. Date of consent<br>Exclude patients with date of consent which is unknown, before 01.01.2013 or in the future. |
| 8. Multiple responses to Dates<br>If multiple responses were given to the dates (of first symptom; first presentation to primary care; referral; diagnosis; treatment start), then use the earliest date. |
| 9. Order of Dates<br>The dates must be in the following order –<br><br>First symptom; first presentation to Primary Care; referral; diagnosis; treatment start.<br><br>If not, check for mistakes. |

10. Date of first symptom
Date of first symptom is defined as date of first symptom from patient data.

11. Date of first presentation
Date of first presentation to Primary Care is defined as (in the order of declining priority):
a) date of first presentation to Primary Care from PCP data;
b) date of first presentation to Primary Care and A&E from PCP data;
c) date of first presentation to Primary Care from patient data.

12. Date of referral
Date of referral is defined as date of referral from PCP data.

13. Date of diagnosis
*Definition*
a) If Registry reports both date of histological confirmation and date of confirming investigation, then use date of histological confirmation.
b) Date of diagnosis (based on patient data, PCP data, specialist data, registry data) is defined as (in the order of declining priority):
- date of diagnosis from registry;
- date of histological confirmation (from specialist data, PCP data);
- date of biopsy (from specialist data, PCP data);
- date of confirming investigation (from specialist data, PCP data);
- date of first hospital admission (from specialist data, PCP data);
- date of MDT confirmation (from specialist data, PCP data);
- date patient was told (from specialist data, PCP data);
- other date of diagnosis (from specialist data, PCP data, patient data);

Choose a Date from a lower level of hierarchy, if the Date from a higher level is after the Date of consent or more than 9 months (=271 days) before the Date of consent.

*Exclusion criteria*

a) Unknown date of diagnosis;
b) Date of diagnosis is after the date of consent;
c) Date of diagnosis is more than 9 months before the Date of consent.

14. Date of treatment start
a) Date of treatment start from patient data is defined as the earliest of the treatment dates for Surgery, Chemo, Radio and Other (e.g. palliative care, participation in a clinical trial, targeted agents like erlotinib and procedures like plueral tap)

b) Date of treatment start (based on registry data, specialist data, patient data) is defined as (in the order of declining priority):
- date of treatment start from registry data,
- date of treatment start from specialist data,
- date of treatment start from patient data,
- anticipated date of treatment from patient data.

15. Imputation of missing day in the date

Imputation rules for missing day (given month and year are known):

a) Set missing day to '16';
b) Consider adjacent dates in a backwards order (from "Treatment" to "First symptom"). For each pair of such adjacent dates: If dates are not in a logical order (e.g. "Treatment" is before "Diagnosis"), but month and year are the same in both dates, and the day was imputed to '16' in one of the dates:
- Recode the day imputed earlier to '16' to the day from the adjacent date.

16. Considering time

If patient gave multiple answers to the "How long did you have symptoms before contacting a doctor?" question, then use the option with the shortest time interval.

17. Delay arranging appointment

If patient gave multiple answers to the "How long did it take to get an appointment with PCP?" question, then use the option with the shortest time interval.

18. Duration of symptoms

If PCP gave multiple answers to the "Duration of symptoms" question, then use the option with the shortest time interval.

19. Definition of Presentation

A. *Define Presentation within a Data Source*

1. Review the free-text for Presentation (Patient, PCP sources) and re-code, if possible.
2. If PCP reports 'Other' as Presentation and at least one symptom (or "Duration of Symptoms") or if Patient reports 'Other' as Presentation and at least one symptom (or date of first symptom or "Consider waiting time" or "Delay arranging appointment"), then re-code the Presentation in the corresponding data source to 'Unknown'- option.
3. In the case of multiple Presentation responses (Patient, PCP sources) - use a single option (in the order of declining priority):
   a) 'VisitPCP and AE',
   b) 'VisitPCP´, 'AE´ (if both 'VisitPCP´ and 'AE´ are given, then re-code as 'VisitPCP and AE'),
   c) 'Unknown',
   d) 'Investigation for another problem' ,
   e) 'Other"

*B. Define Presentation from Alternative Data*

If Presentation hasn't been reported in either of data sources, then define it 'Unknown',

if PCP reports at least one symptom (or "Duration of symptoms"); or if Patient reports

at least one symptom (or date of first symptom or "Consider waiting time" or "Delay arranging

appointment");

C. *Define Presentation from Data Source Hierarchy*

1. In all jurisdictions, except Sweden – use Presentation data from (in the order of declining priority):
   a) PCP data;
   b) Patient data;
2. In Sweden – use Presentation data from Patient data.

20. Patient interval

The Patient interval is defined as (in the order of declining priority):

a) "Date of first presentation to Primary Care" (rule 11) minus "Date of first symptom" (rule 10);
b) If the interval in (a) is unknown or negative: Calculate the interval as the low boundary of "Considering time" (rule 16) plus the low boundary of "Delay arranging appointment" (rule 17);
c) If the interval in (a) is unknown or negative and the interval in (b) is unknown: Calculate the interval as the low boundary of "Duration of symptoms interval" (rule 18).

21. Primary Care interval

The Primary Care interval is defined as "Date of referral" (rule 12) minus "Date of first presentation to Primary Care" (rule 11).

22. Diagnostic interval

a) The Diagnostic interval is defined as "Date of diagnosis" (rule 13) minus "Date of first presentation to Primary Care" (rule 11).

23. Treatment interval

The Treatment interval is defined as "Date of treatment start" (rule 14) minus "Date of diagnosis" (rule 13).

24. Total interval

a) The Total interval is defined as "Date of treatment start" (rule 14) minus "Date of first symptom" (rule 10).

25. Range of Time intervals

The time intervals (Patient, Primary Care, Diagnosis, Treatment, Total) must be in range 0-1 year.

If > 1 year: set the interval to 365 days

If negative: set the interval to 0.

26. Number of visits
If patient gave multiple answers to the "Number of visits" questions, then use the option with a fewer number of visits.

27. Specialist waiting time interval
If patient gave multiple answers to the ""How long did it take to get an appointment with specialist?" question, then use the option with the shortest time interval.

28. Type of treatment
If patient ticked both "Yes" and "No" as answers to the "Type of treatment (Surgery, Chemotherapy, Radiotherapy)" questions, then choose "Yes" answer.

29. Health state
If patient gave multiple answers to the "Health state" question, then use the option with a better health condition.

30. Comorbidity
a) If patient ticked both "Yes" and "No" as answers to the "Comorbidity (Heart disease, Stroke, Lung disease, Diabetes)" questions, then choose "Yes" answer;
b) If both patient and PCP report "Comorbidity", then use the PCP Data.

31. Ethnicity
a) If patient didn't report "Ethnicity", then use the information from (in the order of declining priority):
   - "Ethnicity_Other_Details";
   - "Other main language spoken at home";
   - "The main language spoken at home" (only for Victoria);
   - "The main language spoken at home is the chief one for this jurisdiction"="Yes" given "Main language spoken at home is other than the main one for this jurisdiction"="No";

b) Consider Ethnicity as unknown, if answers to the "Ethnicity" question are multiple and belong to
different categories ( 'white', 'Asian', 'black', 'other').

32. Education
If patient gave multiple answers to the "Education" question, then use the option with a higher level of education.

33. Smoking Current
a) If patient ticked both "Yes" and "No" as answers to the "Smoking Current" question, then use "Yes" answer;
b) If patient hasn't ticked neither "Yes" nor "No, then consider this case as Unknown.

34. Smoking Number

If patient reports "SmokingNumber" as text, then re-code using following rules:

a) Where there is a number smoked /day – accept number;
b) Where a range has been given – take the upper value;
c) Where patient has put 10+ or 20+ - capture this as 11 or 21;
d) Where number of cigarettes smoked in the past and currently being smoked are provided - average the numbers;
e) Non entries code as "." ;
f) Non-smokers (eg, "nil", "N/A") are coded as "0".

35. Smoked ever

a) If patient ticked both "Yes" and "No" as answers to the "Smoking ever" question, then use "Yes" answer;
b) If patient hasn't ticked neither "Yes" nor "No": consider it as "Yes", if patient is a current smoker ("Smoking_Current="Yes"") or has specified a number of cigarettes ("SmokingNumber">0). Otherwise consider this case as Unknown.
c) If patient has ticked "No": recode it to "Yes", if patient is a current smoker ("Smoking_Current="Yes").

36. Nature of referral

a) Review free-text for " Nature of referral" (PCP Data) and re-code, if possible;
b) In the case of multiple responses, use a single option as (in the order of declining priority):

- "Referral for immediate admission";
- "Urgent referral";
- "Less urgent referral";
- "General referral" ;
- "No referral";
- "Other".

37. Refer Public or Private

a) If PCP ticked both "Public" and "Private" as answers to the "Refer Public or Private" question, then use "Private" answer;
b) If PCP hasn't ticked neither "Public" nor "Private", then consider this case as Unknown.

38. Type of referral

If specialist gave multiple responses to the "How was the patient referred…" question, then use a single option (in the order of declining priority):

- "Respiratory clinic";
- "Specialist/consultant";
- "PCP";
- "Other".

| |
|---|
| 39. First Attendance Place<br>If specialist gave multiple responses to the "First Attendance Place" question, then consider this case as Unknown. |
| 40. Stage-TNM<br>a) If specialist gave multiple responses to the "Stage_TNM" question, then use the highest category;<br>b) If registry gave multiple responses to the "Stage_TNM", then use a single option (in the order of declining priority):<br>- stage at time of diagnosis<br>- stage at surgery<br>- stage at oncology<br>c) If "Stage_TNM" is reported by both the specialist and registry, then use the registry data. |

## Appendix C: Supplementary Tables

**C 1:** Classification of lung cancer -specific symptoms reported by patients into cancer specific and non- cancer specific

**Cancer specific symptoms**

| |
|---|
| 1 persistent cough |
| 2 chest infection that wouldn't get better |
| 3 coughing up blood-stained phlegm (sputum) |
| 4 breathlessness |
| 5 chest or shoulder pain |
| 6 a hoarse voice |
| 7 difficulty swallowing |
| 8 swelling of lymph nodes (glands) in my neck |
| 9 ends of fingers becoming larger |
| 10 breast and axilla swelling (in men) |

**Non-cancer specific symptoms**

| |
|---|
| 1 a dull ache or sharp pain when I coughed or took a deep breath |
| 2 pain/discomfort under my ribs |
| 3 face swelling |
| 4 blood clots (thrombosis) |
| 5 pins and needles or numbness in fingers |
| 6 weight loss |
| 7 felt sick/vomiting/nausea/loss of appetite |
| 8 fatigue |
| 9 muscle weakness |
| 10 drowsiness, weakness, dizziness or confusion |
| 11 high temperature (fever) of 38C (100.4F) |
| 12 other |

**C2:** Time intervals (days) depicted as median, 75$^{th}$ and 90$^{th}$ centiles for each of the ten jurisdictions. In Sweden, no data was available on primary care interval

| Intervals | Centiles | Wales | Denmark | Sweden | England | N Ireland | Scotland | Manitoba | Ontario |
|---|---|---|---|---|---|---|---|---|---|
| Patient Interval | Number | 181 | 233 | 172 | 213 | 179 | 169 | 133 | 205 |
| | Median | 21 | 14 | 21 | 17 | 18 | 21 | 25 | 22 |
| | 75th centile | 61 | 53 | 61 | 65 | 60 | 60 | 67 | 61 |
| | 90th centile | 216 | 180 | 214 | 205 | 240 | 267 | 180 | 187 |
| Primary Care interval | Number | 110 | 159 | n/a | 147 | 124 | 119 | 80 | 75 |
| | Median | 20 | 7 | | 11 | 13 | 16 | 30 | 29 |
| | 75th centile | 43 | 20 | | 31 | 51 | 35 | 75 | 73 |
| | 90th centile | 91 | 64 | | 73 | 112 | 90 | 138 | 183 |
| Diagnostic interval | Number | 176 | 229 | 165 | 212 | 170 | 173 | 138 | 212 |
| | Median | 45 | 35 | 28 | 54 | 65 | 42 | 87 | 57 |
| | 75th centile | 108 | 67 | 83 | 100 | 122 | 106 | 147 | 122 |
| | 90th centile | 162 | 162 | 143 | 161 | 281 | 198 | 265 | 331 |
| Treatment interval | Number | 192 | 279 | 190 | 238 | 200 | 187 | 182 | 263 |
| | Median | 43 | 16 | 34 | 22 | 32 | 42 | 19 | 47 |
| | 75th centile | 64 | 25 | 59 | 41 | 48 | 62 | 56 | 70 |
| | 90th centile | 89 | 37 | 77 | 56 | 72 | 90 | 97 | 96 |
| Total interval | Number | 147 | 192 | 147 | 176 | 157 | 143 | 117 | 178 |
| | Median | 116 | 67 | 107 | 114 | 105 | 117 | 127 | 130 |
| | 75th centile | 204 | 116 | 190 | 183 | 227 | 253 | 216 | 216 |
| | 90th centile | 365 | 210 | 329 | 323 | 365 | 365 | 365 | 339 |

**C3:** Data sources used to define dates and percentage of imputed dates

| Type of date | Data sources used to define a date* (%) | | | | Cases with imputed day in a date** (%) |
|---|---|---|---|---|---|
| | Patient | PCP | CST | Registry | |
| First noticing symptoms | 100 | 0 | 0 | 0 | 66 |
| First presentation to health care | 49 | 51 | 0 | 0 | 30 |
| First referral to secondary care | 0 | 100 | 0 | 0 | 1 |
| Diagnosis | 5 | 6 | 8 | 81 | 1 |
| Start of curative or palliative treatment | 55 | 0 | 32 | 13 | 11 |

* based on rules 10-14, supplementary file Appendix B
** based on rule 15, supplementary file Appendix B
*** Registry/CST medical records on date of treatment were not available for 55% patients, therefore an alternative data source (patient survey) was used instead

**C4.** Percentages of negative intervals set to 0, large intervals (>365 days) set to 365 days, and intervals based not on dates

| Type of interval | Negative intervals set to 0 days* (%) | Intervals >365 days set to 365 days* (%) | Intervals where variables other than dates were used (%)** |
|---|---|---|---|
| Patient | <1 | 5 | 29 |
| Primary care | 4 | 2 | 0 |
| Diagnosis | 6 | 5 | 0 |
| Treatment | 6 | <1 | 0 |
| Total | 2 | 9 | 0 |

* based on rule 25, supplementary file Appendix B
* based on rule 20b,c, supplementary file Appendix B

**The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.**

| | Item No. | STROBE items | Location in manuscript where items are reported | RECORD items | Location in manuscript where items are reported |
|---|---|---|---|---|---|
| **Title and abstract** | | | | | |
| | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found | Title and abstract – p 1 and 3 | RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.<br><br>RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.<br><br>RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract. | Abstract – p 3<br><br>Abstract – p 3<br><br>N/A |
| **Introduction** | | | | | |
| Background rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Introduction – p 6 | | |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Introduction – p 6 | | |
| **Methods** | | | | | |
| Study Design | 4 | Present key elements of study design early in the paper | Methods – p 6 | | |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Methods – p 6-8 | | |
| Participants | 6 | *(a) Cohort study* - Give the eligibility criteria, and the | Methods – p 6 – and as reference to | RECORD 6.1: The methods of study population selection (such as codes or | Provided as reference to |

| | | | | | |
|---|---|---|---|---|---|
| | | sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants<br><br>*(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study* - For matched studies, give matching criteria and the number of controls per case | previous paper.<br><br>N/A | algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.<br><br>RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.<br><br>RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage. | previous paper.<br><br>Provided as appendix and in reference to previous paper.<br><br>N/A |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. | Methods – p 6-9 – and as reference to previous paper. | RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided. | N/A |
| Data sources/ measurement | 8 | For each variable of interest, give sources of data and details of methods of assessment (measurement).<br>Describe comparability of assessment methods if there is more than one group | Methods – p 6-9 – and as reference to previous paper. | | |
| Bias | 9 | Describe any efforts to address potential sources of bias | Methods – p 7-8, discussion – p 24-25 – and as reference to | | |

| | | | | | |
|---|---|---|---|---|---|
| | | | previous paper. | | |
| Study size | 10 | Explain how the study size was arrived at | Methods – p 6 – and as reference to previous paper. | | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | Methods – p 6-8 – and as reference to previous paper. | | |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding<br>(b) Describe any methods used to examine subgroups and interactions<br>(c) Explain how missing data were addressed<br>(d) *Cohort study* - If applicable, explain how loss to follow-up was addressed<br>*Case-control study* - If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy<br>(e) Describe any sensitivity analyses | Methods – p 8 – and as reference to previous paper. | | |
| Data access and cleaning methods | | .. | | RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. | N/A |

| | | | | | |
|---|---|---|---|---|---|
| | | | | RECORD 12.2: Authors should provide information on the data cleaning methods used in the study. | Methods – p 7 |
| Linkage | | .. | | RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided. | N/A |
| **Results** | | | | | |
| Participants | 13 | (a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed)<br>(b) Give reasons for non-participation at each stage.<br>(c) Consider use of a flow diagram | Results and as table – p 10-11. Flow diagram in previous paper, referenced. | RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram. | Results – p 10-15 - and as table. Flow diagram in previous paper, referenced. |
| Descriptive data | 14 | (a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate the number of participants with missing data for each variable of interest<br>(c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount) | Results and as table – p 10-15. | | |
| Outcome data | 15 | *Cohort study* - Report numbers of outcome events or summary measures over time<br>*Case-control study* - Report numbers in each exposure category, or summary measures | Results and as table – p 16-23. | | |

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| | | of exposure<br>*Cross-sectional study* - Report numbers of outcome events or summary measures | | | |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(b) Report category boundaries when continuous variables were categorized<br>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Results and as table – p 21-23. | | |
| Other analyses | 17 | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses | Results – p 23. | | |
| **Discussion** | | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | Discussion – p 24 | | |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Discussion – p24-25 | RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported. | Discussion – p24-25 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar | Discussion – p25-28 | | |

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| | | studies, and other relevant evidence | | | |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | Discussion, conclusion – p25-29. | | |
| **Other Information** | | | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Funding statement – p 31 | | |
| Accessibility of protocol, raw data, and programming code | | .. | | RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code. | Availability of data and material statement – p 31 |

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.