European Journal of Cancer 87 (2017) 113–121

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Time to diagnosis and treatment for cancer patients in the Netherlands: Room for improvement?

Charles (C.W.) Helsper*[,1], Nicole (N.F.) van Erp [1], Petra (P.H.M.) Peeters, Niek (N.J.) de Wit

Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, P.O. Box 85500, 3508 GA Utrecht, The Netherlands

Received 24 July 2017; received in revised form 26 September 2017; accepted 3 October 2017
Available online 13 November 2017

KEYWORDS
Primary care;
General practice;
Cancer;
Diagnosis;
Duration;
Delay;
Interval;
Netherlands;
Diagnostic delay

Abstract ***Background & aim:*** Reducing the duration of the diagnostic cancer care pathway is intensively pursued. The aim of this study was to chart the diagnostic pathway for the five most common cancers in the Netherlands.
Methods: A retrospective cohort study using cancer patients' anonymised primary care data (free text and coded) linked to the Netherlands Cancer Registry. We determined the median duration of the following: 1. Primary care intervals (IPCs): the first cancer-related general practitioner consultation to referral, 2. Referral intervals (IRs): referral to diagnosis, 3. Treatment intervals (ITs): diagnosis to treatment and the overarching intervals, 4. Diagnostic intervals (IDs): IPC and IR combined and 5. Health care intervals (IHCs): IPC, IR and IT combined.
Results: For 465, 309, 197, 237 and 149 patients diagnosed with breast-, colorectal-, lung-, prostate cancer and melanoma, respectively; median IPC, IR and ID durations were shortest for breast cancer and melanoma (ID duration 7 and 21 days, respectively), intermediate for lung- and colon cancer (ID duration 49 and 54 days) and the longest for prostate cancer (ID duration 137 days). For all cancers, the duration of intervals increased steeply for the 10–25% with longest durations. For colorectal cancer, increasing ID durations showed increasing proportions of time attributable to primary care (IPC).
Conclusion: Approximately 10–25% of cancer patients show substantially long duration of diagnostic intervals. Reducing primary care delay seems particularly relevant for colorectal cancer.

* *Corresponding author.*
E-mail addresses: C.W.Helsper-2@umcutrecht.nl (C.(C.W.) Helsper), N.F.vanErp@umcutrecht.nl (N.(N.F.) van Erp), P.H.M.Peeters@umcutrecht.nl (P.(P.H.M.) Peeters), N.J.deWit@umcutrecht.nl (N.(N.J.) de Wit).
[1] First and second author share first authorship.

https://doi.org/10.1016/j.ejca.2017.10.003
0959-8049/

1. Introduction

Despite improving treatment outcomes, cancer is a major health problem with high morbidity and mortality rates worldwide. Prognosis largely depends on tumour stage at diagnosis [1,2]. Early diagnosis and treatment is considered vital to improve patient outcome and to reduce time spent in insecurity for patients [3,4]. Even though the association between time intervals in the diagnostic pathway and clinical outcomes is complex and remains debated, evidence suggests worse outcomes after longer diagnostic intervals [5,6]. Optimising the diagnostic pathway from first presentation to diagnosis and start of treatment, usually interpreted as shortening the diagnostic phase, has therefore been a main objective of health care organisations involved in cancer care worldwide.

The Aarhus statement defines several key time points and associated intervals in the diagnostic pathway [7]. The primary care interval (IPC) is the time between the first cancer symptom related contact with the general practitioner (GP) and its corresponding referral to secondary care. The referral interval (IR) can be defined as the time from referral to histological diagnosis and the treatment interval (IT) is defined as the time from diagnosis to initiation of the treatment. Overarching intervals are the diagnostic interval (ID): the time from the first presentation to the GP to diagnosis and the health care interval (IHC): the time from the first presentation to the GP to initial treatment.

For some countries in Europe, the duration of several of these intervals has been charted. All diagnostic intervals, but particularly the IPC, are usually shorter for cancers presenting with visible or palpable symptoms such as breast cancer and melanoma [4,8–11]. For other countries, such as the Netherlands, the duration of these intervals is unknown.

International comparison of the duration of IDs in different health care systems and cultural environments is important to identify system-, disease- and patient-related factors that contribute to an unnecessarily prolonged patient journey. Analyses of cancer survival rates show that health care systems with a gatekeeping role of the GP have a significantly lower relative cancer survival than systems without a gatekeeper function [12]. This observation was followed by a study addressing the question if serious problems in cancer survival are partly rooted in gatekeeper principles [13]. This ecologic analysis of relatively old data showed that having a gatekeeper system was associated with lower 1-year survival in health care systems with primary care-based gatekeeping.

These findings suggest that a primary care-based gatekeeper system could delay cancer diagnosis as a result of a long duration of the ID and the underlying IPC and IR.

The health care system in the Netherlands is based on a strict gatekeeper role of the GP, which means secondary care facilities are almost exclusively accessible through referral from primary care (see Box 1). Exploring the duration of the diagnostic pathway in the Netherlands and the contribution of primary care to this pathway, generate relevant information on international differences in the duration of the diagnostic pathway. This provides the opportunity to distinguish underlying mechanisms of delay, including system-, disease- and patient-related delay.

Therefore, we aim to assess the duration of the diagnostic pathway and its underlying intervals for the five most frequently occurring cancer types in the Netherlands: Colorectal-, breast-, lung-, prostate cancer and melanoma, with a particular focus on the potential role of the GP in the diagnostic process.

2. Methods

2.1. Design

We conducted a retrospective cohort study using routine primary care data from the Julius General Practitioners Network (JGPN) database, linked to the data of the Netherlands Cancer Registry (NCR). We used a trusted third-party linkage procedure to comply with privacy regulations of the Dutch law. The JGPN, the NCR and the linkage procedure are described in detail elsewhere [18].

Box 1. Organisation and characteristics of primary care in the Netherlands

Primary care in the Netherlands

- All Dutch citizens are listed with a GP.
- GP services are free: costs for GP encounters are covered by basic insurance, which is obligatory for every citizen by law.
- The GP is the gatekeeper to secondary care.
- At the time of the study there were approximately 8900 employed GPs in the Netherlands [14].
- The practice norm for the number of patients was 2350 patients per GP practice [15].
- For 75% of Dutch citizens, the nearest GP was situated within one kilometre, and for less than 1% of the people, this distance was longer than five kilometers [16].

Primary care and cancer

- On average, a full time Dutch GP sees 25 new adult cancer patients each year (including all types of skin cancer) [17].
- In the study period, a national screening program for breast cancer and cervical cancer was available in the Netherlands. For colorectal cancer a national screening programme started in 2014.

The Research Ethics Committee of the University Medical Center Utrecht judged the study exempt from assessment because this study uses only anonymised patient data.

2.2. Population

The JGPN is a database containing routine care registrations of 200 GPs with 300,000 patients. Its population is considered representative for the Dutch population [19]. The NCR is a population-based registry with detailed diagnostic and therapeutic data of over 95% of Dutch cancer patients since 1989 [20].

The linked data set contains anonymous coded and free text information. In the JGPN, free text data of consultations are available for patient symptoms, physical examination, working diagnosis and initiated policy. Coded information is available for working diagnoses, using the International Classification of Primary Care 1 (ICPC-1) coding system [21] and for medication. For each consultation the date is registered. The NCR is tumour based and includes date and histological details of cancer diagnoses such as disease stage, malignancy grade, morphology, localisation, date and type of the first treatment. Cancer type is coded using the International Classification of Diseases for Oncology (ICD-O) coding system.

2.3. Case selection

All patients aged 20–90 occurring in both registries (JGPN and NCR) with a corresponding ICPC and ICD-O code for breast-, colorectal-, lung- or prostate cancer between 2007 and 2011 were included. Because of the relatively low incidence rate, we extracted data on melanoma from 2004 to 2011.

Based on free text information, we selected patients who presented to the GP with symptoms, which were directly or indirectly linked to the cancer and were referred by the GP. We also selected breast cancer patients detected through screening. Of the five most common cancer types, only breast cancer had a fully implemented screening program in the Netherlands during the observation period. Women aged 50–75 years receive an invitation for mammography every 2 years and are referred for diagnostic work-up by their GP in case of a suspicious finding. National colorectal cancer screening started several years after our observation period.

2.4. Data collection

The relevant duration, disease- and patient-related data were collected from the JGPN and NCR by medically trained researchers with experience in the primary care field. Data were manually checked from 5 years before the date of histological diagnosis up to 1 year after the diagnosis. We included 1 year after diagnosis because it may contain information on the pathway and explain some discrepancies between diagnostic date in the NCR and diagnostic date in the JGPN. Backdating diagnostic dates in the GPs registration is mandatory according to registration guidelines, but may be forgotten.

From the JGPN, we extracted baseline patient characteristics (age and gender), signs and symptoms and date of the first consultation and referral. From the NCR, we extracted details of cancer diagnoses and date of diagnosis and treatment initiation.

Definitions of the intervals were in agreement with the key time points of the Aarhus statement (Fig. 1) [7]. The date of the first cancer-related GP consultation was defined as the first contact (physical or telephone) with the GP for suspected cancer-related signs or symptoms. The first presentation of more and less specific cancer-related complaints to the GP was determined by scrutinising the free text of all consultations preceding the diagnosis. In case of doubt concerning the first cancer-related sign or symptom presentation, the consultation with the complaint that eventually led to the diagnosis was chosen. For prostate cancer, the start of IPC was defined as; presentation of symptoms or signs (including elevated prostate specific antigen) leading to diagnosis. For breast cancer screening, the start of IPC was defined as the day that the GP receives notification of a suspicious screening result (mammogram) for one of his patients.

The date of referral was defined as the moment when the responsibility for the patient was transferred from a GP to secondary care. In case of multiple referrals, or cross-referrals in secondary care, the first referral for further exploration of the cancer-related symptom(s) was chosen.

Date of diagnosis was retrieved from the NCR data. The NCR uses the hierarchy for the time of diagnosis, as provided by the European Network of Cancer Registries (www.encr.eu/images/docs/recommendations/incideng.pdf), which is in accordance with the preferred date of diagnosis in the Aarhus Statement [7]. The NCR receives diagnostic details, including the date of histological confirmation, for all malignant diagnoses from the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA). PALGA receives data from histological and cytological biopsies from 99% of all laboratories in the Netherlands. The NCR also receives diagnostic details from clinical records in the hospitals, which are used if details from PALGA are unavailable. For over 98% of the included patients with breast-, colorectal-, prostate cancer and melanoma, and for 64% of the lung cancer patients in this study, the date of diagnosis was the date of the histological confirmation of the primary tumour.

The date of treatment initiation denotes the date of start of therapy as registered in the NCR. The NCR uses the hospital medical records to retrieve this information. The date of treatment is absent in case of no initiated therapy. Only for melanoma, in case of two consecutive treatments,

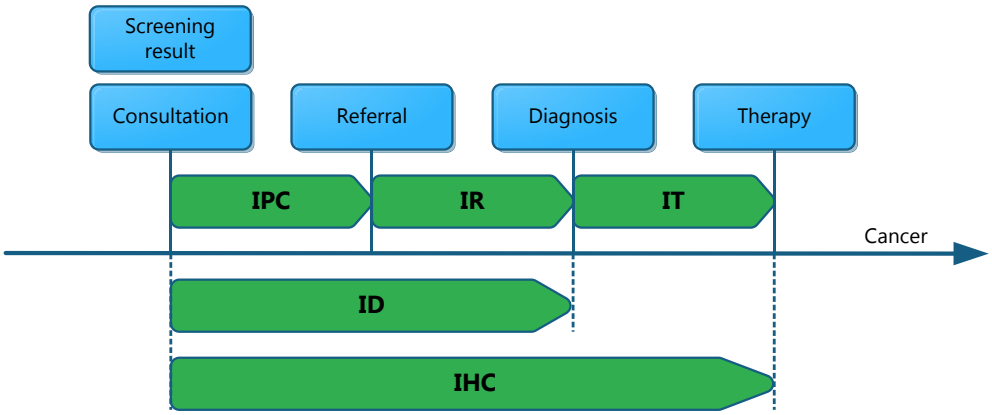

Fig. 1. Overview of the cancer diagnostic pathway and its intervals. IPC, primary care interval; IR, referral interval; IT, treatment interval; ID, diagnostic interval; IHC, health care interval.

the second was considered as the date of treatment, presuming the first date concerns the diagnostic excision.

The pathways for melanoma patients were stratified according to diagnostic pathway: 1. Referred by the GP for diagnostic excision or 2. Diagnostic excision performed by the GP. This policy was determined based on the free text information. The pathways for breast cancer patients were described separately for symptomatic women who presented to the GP and those found through the national screening program.

2.5. Statistical analysis

Descriptive statistics were used to describe the baseline characteristics of the study population. We report both the median (interquartile interval [IQI]) duration of the separate (IPC, IR and IT) and overarching (ID and IHC) intervals. The cut-off for the 25% and 10% of patients with the longest durations are defined below as 'P75' and 'P90', respectively. Same-day proceedings were counted as 1 day; therefore, we consistently added 1 day to all durations.

The proportion of ID attributable to primary care (IPC) was determined for each quartile of ID duration. This proportion IPC of ID was expressed as median percentages in each consecutive quartile of ID. Analyses were performed in SPSS, version 22.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Baseline characteristics

We found 465, 309, 197, 237 and 149 patients with breast-, colorectal-, lung-, prostate cancer and melanoma, respectively, presenting to and referred from primary care. These patients include 61% (lung cancer), 71% (prostate cancer and melanoma), 73% (colorectal cancer) and 77% (breast cancer) of all patients registered with these cancers in both the JGPN and the NCR in the study period. Patient characteristics are described in Table 1. A list of the cancer-related signs and symptoms presented at the first GP consultation (start IPC) is available in Supplementary materials.

For breast cancer, 164 of 465 (35%) were found through screening. Breast cancer patients diagnosed through screening were slightly older and had more favourable tumour stages.

Of the 149 melanoma patients, 75% was referred to secondary care for diagnostic excision of a suspicious pigmented lesion. In 25% of melanoma patients the initial (diagnostic) excision was performed by the GP. They were relatively young patients, and their lesions were generally not located on visible body parts. There was no difference in tumour stage distribution in the two melanoma diagnostic pathways.

Table 1
Characteristics of the included cancer patients at the start of the diagnostic interval.

Characteristics	Breast cancer total n = 465		Colorectal cancer	Lung cancer	Prostate cancer	Melanoma
	Screening	Symptom				
Population (N)	164	301	309	197	237	149
Gender						
Female N (%)	164 (100)	301 (100)	154 (49.8)	91 (46.2)	0 (0.0)	82 (55.0)
Age						
Mean ± SD	60.9 ± 7.9	57.2 ± 15.5	66.7 ± 12.2	66.5 ± 10.7	67.1 ± 7.6	55.2 ± 15.6
Median (IQI)	61.0 (53.0–67.0)	54.0 (45.0–69.0)	68.0 (60–75.5)	68.0 (59.0–75.0)	67.0 (62.0–72.0)	55.0 (43.0–66.0)

SD, standard deviation; IQI, interquartile interval.

3.2. Duration of the intervals

The date of first consultation, referral and diagnosis was available for over 95% of patients for all five cancer types. The date of treatment was not available for 5% of breast and colorectal cancer patients and 20–42% of melanoma, lung- and prostate cancer patients.

Median duration (IQI, P90 value) for each interval for all cancer types can be found in Table 2 and Fig. 2. Distribution of duration of all intervals was highly right skewed for all cancers.

IPC: Median duration of IPC varied from 1 day (breast cancer and melanoma), to 2 weeks (lung and prostate cancer). Over 75% (<P75) of symptomatic breast cancer and melanoma patients were referred on the same day of presentation to the GP.

IR: Median duration of IR ranged from 6 days (breast) to 51 days (prostate).

IT: Median duration of IT was between 21 and 29 days, except for prostate cancer (65 days).

Median ID and IHC duration ranges were 7–137 days and 29–237 days, respectively. Medians and P75 values were the highest for prostate cancer, lowest for breast cancer and melanoma and in between for colorectal cancer and lung cancer.

The median proportions of ID duration attributable to primary care (IPC), for the consecutive quartiles of ID duration, are shown in Fig. 3 for all cancer types. Only for colorectal cancer, the proportion of ID duration attributable to IPC duration increased for longer ID durations with a median of 14% of ID duration attributable to IPC in the 0–25th percentile, to 73% of ID in IPC in the 75–100th percentile of ID duration.

Table 2
Duration of the different intervals of the diagnostic pathway in days.

	IPC	IR	IT	ID	IHC
Breast - symptomatic	**n = 295**	**n = 295**	**n = 284**	**n = 301**	**n = 284**
Median	1	6	21	7	29
IQI	(1–1)	(3–10)	(15–28)	(3–13)	(22–43)
P90 value	4	20	40	36	61
Range	1–267	1–583	1–98	1–583	7–609
Breast - screening	**n = 158**[a]	**n = 158**	**n = 164**	**n = 164**	**n = 164**
Median	1	8	22	10	32
IQI	(1–4)	(5–12)	(16–30)	(6–15)	(24–44)
P90 value	8	23	40.5	24.5	62
Range	1–16	1–172	1–107	2–174	14–183
Colorectal	**n = 309**	**n = 309**	**n = 295**	**n = 309**	**n = 295**
Median	8	26	27	54	82
IQI	(1–59)	(13–54)	(15–39)	(21–116)	(50–152)
P90 value	219	96	50	316	313
Range	1–1177	1–864	1–78	1–1226	1–1244
Lung	**n = 197**	**n = 197**	**n = 139**	**n = 197**	**n = 139**
Median	13	21	22	49	76
IQI	(2–36)	(9–51)	(9–38)	(23–83)	(49–117)
P90 value	66	93	56	162	187
Range	1–484	−22[b]–250	1–105	3–513	14–563
Prostate	**n = 237**	**n = 237**	**n = 159**	**n = 237**	**n = 159**
Median	14	51	65	137	237
IQI	(3–153)	(28–203)	(34–92)	(44–639)	(124–734)
P90 value	637	769	129	1310	1371
Range	1–1631	1–1825	1–811	5–1985	8–2040
Melanoma referred	**n = 107**	**n = 107**	**n = 92**[c]	**n = 111**	**n = 92**[c]
Median	1	20	35	21	57
IQI	(1–1)	(9–43)	(22–46)	(9–50)	(37–85)
P90 value	15	61	59	106	148
Range	1–996	1–609	1–108	1–996	4–1020
Melanoma by GP	**n = 32**[d]	n.a.	**n = 23**[c]	**n = 38**	**n = 23**[c]
Median	8.5	n.a.	29	17	47
IQI	(4–35)	n.a.	(19–39)	(8–65)	(28–92)
P90 value	214	n.a.	51	229	170
Range	1–1289	n.a.	8–419	1–1291	20–1327

IPC, primary care interval; IR, referral interval; IT, treatment interval; ID, diagnostic interval; IHC, health care interval; IQI, interquartile interval; GP, general practitioner; n.a., not applicable.

[a] Duration from notification at GP of suspicious finding in screening programme to referral by GP.

[b] Referral from primary care after diagnosis in secondary care.

[c] IT and IHC are based on the second treatment date. Therefore, these analyses exclude the 11% of melanoma cases for whom the diagnostic excision might have been the therapeutic excision (i.e. patients with biopsy with free demarcation may be left out of this analysis).

[d] Duration from first consultation to diagnostic excision procedure by GP.

4. Discussion

For all cancers, a highly right skewed distribution of duration demonstrated that a majority of patients pass through the diagnostic pathway fairly quick. However, for 10–25% of cancer patients, the total ID and the time in primary care (IPC) were relatively long, which could indicate clinically relevant delay. For colorectal cancer, long duration of ID was associated with a relatively high proportion of time spent in primary care (IPC) compared to the other cancer types.

Our findings are in accordance with previous reports suggesting that the primary care interval is shorter for cancers presenting with visible or palpable symptoms such as breast cancer and melanoma [9].

For breast cancer and melanoma, the median duration of IPC (1 day [IQI 1–1]) was comparable to the shortest durations described for Western European countries [8,9,22–24]. It also indicates fairly good compliance to referral guidelines in the Netherlands, which advocate immediate referral in case of potential cancer-related symptoms [25,26]. With 50% of lung cancer patients referred within 2 weeks, our results are favourable compared with Sweden (median 28 days) [27] and the United Kingdom (UK) (median 52 days) [28].

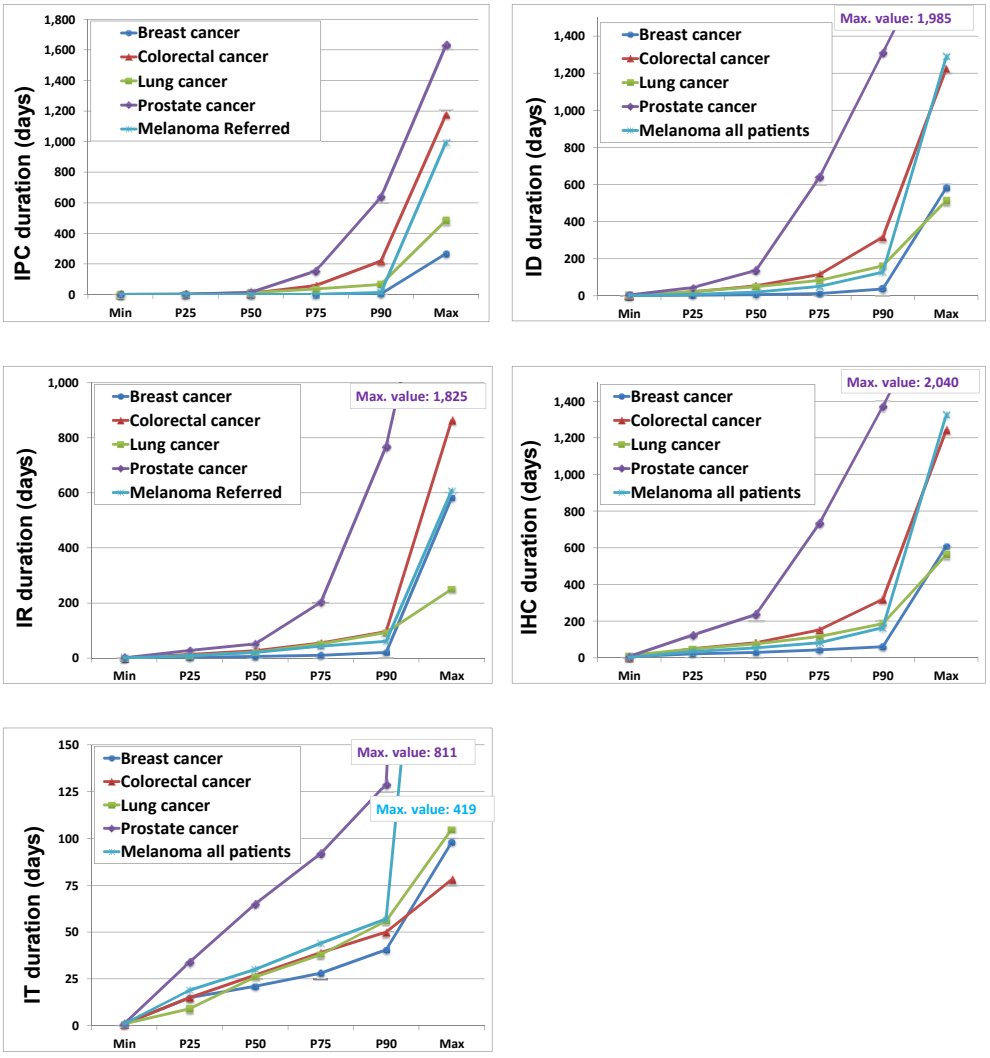

Fig. 2. Phase-related duration for symptomatic patients with five common cancers. IPC, primary care interval; IR, referral interval; IT, treatment interval; ID, diagnostic interval; IHC, health care interval; Min, minimum value; P25, 25th percentile; P50, 50th percentile (median); P75, 75th percentile; P90, 90th percentile; Max, maximum value.

For colorectal cancer, the median duration of the IPC was 8 days (IQI 1–60), which was shorter than what we observed in our previous study (median 14 days, IQI 0–61) [29]. Recent studies from the UK (median 6 days, IQI 0–29) [9] and Denmark (median 0 days, IQI 0–6) [8] show comparably short durations. For prostate cancer, the median duration of the IPC was 14 days (IQI 3–153). In the literature, duration of IPC was rarely studied. This is partly explained by the difficulty to determine the first presentation of symptoms. Hansen *et al.* [8] studied the time interval from the first presentation to initiation of a diagnostic investigation and found a median duration of 0 days (IQI 0–6). This is not comparable to our results, as we studied time up to the referral into secondary care. Studies on the time from consultation to prostate cancer diagnosis found a median duration of 73 days (IQI 41–144) [30], which is shorter than the median duration of ID (i.e. 137 days, IQI 44–639) found in our study.

Using routine care data has limitations, including incomplete reporting and the need for interpretation by experts [18]. Since routine care data are recorded for care purposes, they only contain what is considered clinically important by the GP. The absence of registrations of history taking or physical examination in the free text data does not mean that these findings were not presented, checked or asked for.

Consequently, finding the 'first presentation with a cancer-related symptom' can be challenging, also because the association between common symptoms and cancer (such as cough for lung cancer) can sometimes be questioned. Even though data extraction was performed and discussed by a team of researchers with primary care experience, this challenge may have influenced our findings. Health care systems may change over time, which could potentially affect the duration of the diagnostic process. However, no substantial changes, such as the implementation of screening programs or major

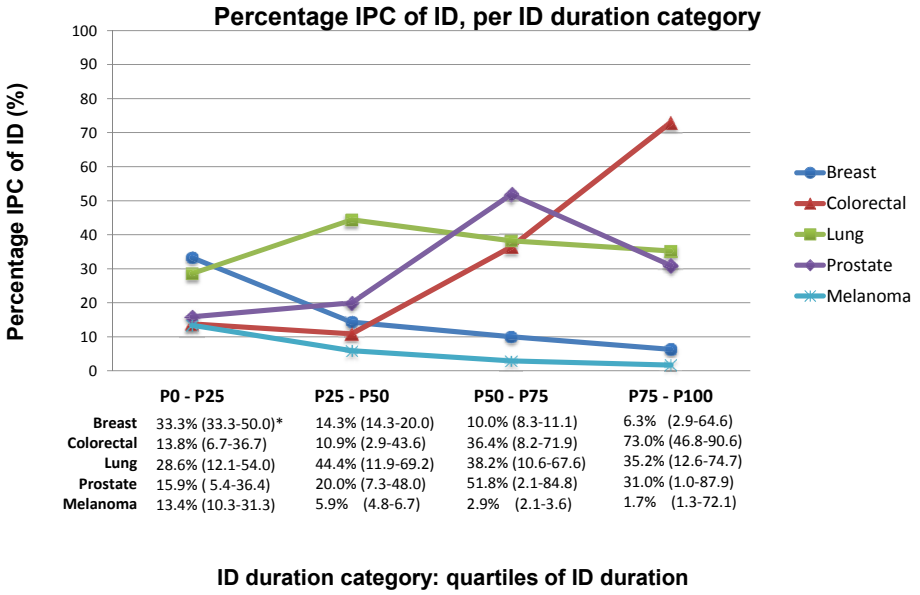

Fig. 3. Percentage of diagnostic duration (ID) attributable to primary care (IPC), for symptomatic cancer patients presenting to primary care. *For each quartile of ID duration (P0–P25 represents the shortest ID duration, P75–P100 represents the longest ID duration), the median percentage of ID duration attributable to the IPC is shown, with IQI. A low percentage means that a low percentage of the diagnostic interval duration is attributable to IPC. IPC, primary care interval; IR, referral interval; IT, treatment interval; ID, diagnostic interval; IHC, health care interval; P, percentile; IQI, interquartile interval.

changes in diagnostic facilities, occurred during the study period (2007–2011).

When using linked data sets based on the corresponding diagnoses and patient data, cancer patients may be missed because of missing diagnoses in either of the linked data sets or linkage flaws resulting from the probabilistic linkage method used. Linkage flaws are unlikely to result in a selective population, but missing diagnosis codes in the JGPN or the NCR are potentially related to the duration of intervals with a main risk of underestimation of duration. Underestimation could result from missing less advanced (hard to detect) cancer stages because advanced cancer with reputed (alarm) symptoms is more likely to be registered with a corresponding cancer diagnosis. Also, longer referral intervals are more likely to lead to omit the mandatory update of the diagnosis codes by the GPs registration. Missing diagnoses in the NCR are rare, but they can be related to the absence of diagnostic information from the hospital. This may be related to old age, which could be associated with longer time to diagnosis.

Furthermore, a small minority of deceased patients (<1%) could not be included in the linkage process because their data were not available in part of the extractions of one of the primary care Electronic Health Registration Systems in the JGPN. More serious illness in this population could have led to an underestimation of duration if long duration induced death, whereas overestimation would occur if a higher prevalence of alarm symptoms speeds up the diagnostic and therapeutic process.

Finally, although routine care data provide an accurate representation of proceedings in health care, information on the patient interval (first cancer symptom to GP consultation) seems unreliable. This interval is relevant for the time to diagnosis, but must be studied otherwise.

The use of routine primary care data (JGPN) also has several strengths. The availability of free text information provides a high density of information, and both symptoms and policy can be determined in more detail as compared with coded data. Furthermore, using routine care data provides a direct representation of daily practice. Data are registered 'on the spot' for a long period of time, therefore preventing recall bias, unlike other studies that use questionnaires for estimating duration [31–34].

Linkage with the NCR data provided accurate diagnostic and therapeutic data. This prevents inclusion of false-positive diagnoses, which have been shown to occur in up to 49% of coded cancer diagnoses reported in routine care data [18].

Differences in the organisation of health care systems have been linked to differences in duration of the diagnostic pathway [3], and gatekeeper systems have been linked to reduced cancer survival [13]. As 85% of cancer cases present to the GP first, early recognition in primary care is paramount to early diagnosis [22]. In primary care, follow-up of complaints is an important diagnostic tool to differentiate serious from benign disease. Therefore, some time spent in primary care (IPC) is inherent to gatekeeper systems. Our findings show that for most cancers and most patients a limited

proportion of time to diagnosis (ID) is attributable to primary care (IPC). However, for 10–25% of cancer patients, IPC is disproportionately long. Furthermore, for colorectal cancer patients, the proportion of ID duration attributable to primary care increases for longer ID durations.

Beside system characteristics, patient-, presentation- and disease characteristics may influence the duration of the diagnostic pathway. Presentation and disease characteristics interact because the development of symptoms differs for slow and fast growing tumours. The harder to identify and probably slower growing cancers often have a multitude of alternative diagnoses and symptoms with relatively low predictive values. Particularly for these cancers, gatekeeper systems rely on primary care to optimise efficiency and safeguard sufficient diagnostic capacity in secondary care, thereby preventing delay after referral. Consequently, this challenging balance between excessive burden for both patients and health care, and not delaying cancer patients in need of diagnosis, will have to remain a focus for continuing improvement and debate. Further profiling those 10–25% cancer patients with the longest durations and assessing the association between patient, presentation and disease characteristics and duration of the intervals may provide starting points for more targeted approaches to reduce delay.

Finally, even though 10–25% of cancer patients can benefit substantially from reducing the time to referral in primary care (IPC), for most cancers and most patients, reducing the time from referral to diagnosis (IR) seems most pressing. This is not just because of the proportional preponderance of IR but mainly because this waiting time is often spent in fear.

5. Conclusions

For all cancers, except prostate cancer, the majority of symptomatic patients seem to experience timely referral by the GP, diagnostic investigation and treatment. There is room for improvement though; future focus should be on profiling the 10–25% of cancer patients who show substantially long duration of primary care and referral interval, to enable targeted approaches to prevent unnecessary delay.

Funding

This work was supported by the Dutch Cancer Society (KWF), project number: UU2014-7116, and The Netherlands Organization for Health Research and Development (ZonMw), project number: 80-83910-98-13031.

Conflict of interest statement

None declared.

Acknowledgements

The authors thank all clinical researchers involved in data collection.

They thank the registration team of the Netherlands Comprehensive Cancer Organisation (IKNL) and particularly Dr Janneke Verloop, for the collection of data for the Netherlands Cancer Registry as well as IKNL staff for scientific advice. They thank the GPs in the Utrecht area participating in the Julius General Practitioners Network for sharing their anonymised EHR data and Julia Velikopolskaia and Nicole Boekema of the JGPN for their assistance in extracting data and the linkage procedures.

This work was supported by the Dutch Cancer Society (KWF), project number: UU2014-7116, and The Netherlands Organization for Health Research and Development (ZonMw), project number: 80-83910-98-13031. These funding sources had no role in collection, analysis and interpretation of data.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejca.2017.10.003.

References

[1] Richard MA, Grob JJ, Avril MF, Delaunay M, Thirion X, Wolkenstein P, et al. Melanoma and tumor thickness: challenges of early diagnosis. Arch Dermatol 1999;135(3):269–74. https://doi.org/10.1001/archderm.135.3.269.

[2] Tørring ML, Frydenberg M, Hansen RP, Olesen F, Hamilton W, Vedsted P. Time to diagnosis and mortality in colorectal cancer: a cohort study in primary care. Br J Cancer 2011;104(6):934–40. https://doi.org/10.1038/bjc.2011.60.

[3] Neal RD. Do diagnostic delays in cancer matter? Br J Cancer 2009;101(Suppl. 2):S9–12. https://doi.org/10.1038/sj.bjc.6605384.

[4] Neal RD, Din NU, Hamilton W, Ukoumunne OC, Carter B, Stapley S, et al. Comparison of cancer diagnostic intervals before and after implementation of NICE guidelines: analysis of data from the UK General Practice Research Database. Br J Cancer 2014;110:584–92. https://doi.org/10.1038/bjc.2013.791.

[5] Neal RD, Tharmanathan P, France B, Din NU, Cotton S, Fallon-Ferguson J, et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Syst Rev Br J Cancer 2015;112(Suppl. 1):S92–107. https://doi.org/10.1038/bjc.2015.48.

[6] Tørring ML, Murchie P, Hamilton W, Vedsted P, Esteva M, Lautrup M, et al. Evidence of advanced stage colorectal cancer with longer diagnostic intervals: a pooled analysis of seven primary care cohorts comprising 11,720 patients in five countries. Br J Cancer 2017;117(6):888–97. https://doi.org/10.1038/bjc.2017.236.

[7] Weller D, Vedsted P, Rubin G, Walter FM, Emery J, Scott S, et al. The Aarhus statement: improving design and reporting of studies on early cancer diagnosis. Br J Cancer 2012;106(7):1262–7. https://doi.org/10.1038/bjc.2012.68.

[8] Hansen RP, Vedsted P, Sokolowski I, Søndergaard J, Olesen F. Time intervals from first symptom to treatment of cancer: a cohort study of 2,212 newly diagnosed cancer patients. BMC Health Serv Res 2011;11(1):284. https://doi.org/10.1186/1472-6963-11-284.

[9] Lyratzopoulos G, Saunders CL, Abel GA, McPhail S, Neal RD, Wardle J, et al. The relative length of the patient and the primary care interval in patients with 28 common and rarer cancers. Br J Cancer 2015;112(Suppl. 1):S35–40. https://doi.org/10.1038/bjc.2015.40.

[10] Baughan P, O'Neill B, Fletcher E. Auditing the diagnosis of cancer in primary care: the experience in Scotland. Br J Cancer 2009; 101(Suppl. 2):S87–91. https://doi.org/10.1038/sj.bjc.6605397.

[11] Din NU, Ukoumunne OC, Rubin G, Hamilton W, Carter B, Stapley S, et al. Age and gender variations in cancer diagnostic intervals in 15 cancers: analysis of data from the UK Clinical Practice Research Datalink. PloS One 2015;10(5), e0127717. https://doi.org/10.1371/journal.pone.0127717.

[12] Berrino F, De Angelis R, Sant M, Rosso S, Bielska-Lasota M, Coebergh JW, et al., EUROCARE Working Group. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995–1999: results of the EUROCARE-4 study. Lancet Oncol 2007;8:773–83.

[13] Vedsted P, Olesen F. Are the serious problems in cancer survival partly rooted in gatekeeper principles? An ecologic study. Br J Gen Pract 2011;61(589):508–12. https://doi.org/10.3399/bjgp11X588484.

[14] Annual GP monitoring report. NIVEL (Netherlands institute for health services research) primary care database (n.d.). Retrieved September 21, 2017, from: https://www.nivel.nl/databank. Accessible from English website: https://www.nivel.nl/en/databases-and-panels.

[15] Nederlandse Zorgautoriteit (NZa). Circulaire Vaststelling beleid huisartsenzorg en multidisciplinaire zorg [in Dutch]. https://www.nza.nl/regelgeving/circulaires [accessed 21 September 2017].

[16] Data of Statistics Netherlands (CBS). Huisarts voor meeste mensen dichtbij huis [in Dutch]. https://www.cbs.nl/nl-nl/nieuws/2009/22/huisarts-voor-meeste-mensen-dichtbij-huis [accessed 21 September 2017].

[17] Korevaar JC, Heins MJ, Donker G, Rijken M, Schellevis F. Oncologie in de huisartsenpraktijk. Huisarts Wet 2013;56(1):6–10.

[18] Sollie A, Roskam J, Sijmons RH, Numans ME, Helsper CW. Do GPs know their patients with cancer? Assessing the quality of cancer registration in Dutch primary care: a cross-sectional validation study. BMJ Open 2016;6(9), e012669. https://doi.org/10.1136/bmjopen-2016-012669.

[19] Rutten FH, Zuithoff NP, Hak E, Grobbee DE, Hoes AW. Beta-blockers may reduce mortality and risk of exacerbations in patients with chronic obstructive pulmonary disease. Arch Intern Med 2010; 170(10):880–7. https://doi.org/10.1001/archinternmed.2010.112.

[20] Netherlands Comprehensive Cancer Organisation (IKNL). Werkwijze [in Dutch]. http://www.cijfersoverkanker.nl/werkwijze-13.html [accessed 21 March 2016].

[21] Lamberts H, Wood M, editors. ICPC. International classification of primary care. Oxford: Oxford University Press; 1987.

[22] Neal RD, Allgar VL. Sociodemographic factors and delays in the diagnosis of six cancers: analysis of data from the "National Survey of NHS Patients: Cancer". Br J Cancer 2005;92(11): 1971–5. https://doi.org/10.1038/sj.bjc.6602623.

[23] Robertson R, Campbell NC, Smith S, Donnan PT, Sullivan F, Duffy R, et al. Factors influencing time from presentation to treatment of colorectal and breast cancer in urban and rural areas. Br J Cancer 2004;90(8):1479–85. https://doi.org/10.1038/sj.bjc.6601753.

[24] Brochez L, Verhaeghe E, Bleyen L, Naeyaert J. Time delays and related factors in the diagnosis of cutaneous melanoma. Eur J Cancer 2001;37(37):843–8.

[25] de Bock GH, Beusmans GHMI, Hinloopen RJ, Corsten MC, Salden NMA, Scheele ME, et al. NHG-Standaard Diagnostiek van mammacarcinoom (Tweede herziening). Huisarts Wet 2008; 51(12):598–609.

[26] IKNL. Landelijke richtlijn Melanoom. 2016. Retrieved mach 22, 2016, from: http://www.oncoline.nl/melanoom.

[27] Lövgren M, Leveälahti H, Tishelman C, Runesdotter S, Hamberg K. Time spans from first symptom to treatment in patients with lung cancer – the influence of symptoms and demographic characteristics. Acta Oncol 2008;47(3):397–405. https://doi.org/10.1080/02841860701592392 (Stockholm, Sweden).

[28] Barrett J, Hamilton W. Pathways to the diagnosis of lung cancer in the UK: a cohort study. BMC Fam Pract 2008;9:31. https://doi.org/10.1186/1471-2296-9-31.

[29] Van Hout AMGH, de Wit NJ, Rutten FH, Peeters PHM. Determinants of patient's and doctor's delay in diagnosis and treatment of colorectal cancer. Eur J Gastroenterol Hepatol 2011;23(11): 1056–63. https://doi.org/10.1097/MEG.0b013e32834c4839.

[30] Baade PD, Gardiner RA, Ferguson M, Youlden DR, Aitken JF, Yaxley J, et al. Factors associated with diagnostic and treatment intervals for prostate cancer in Queensland, Australia: a large cohort study. Cancer Causes Control 2012;23(4):625–34. https://doi.org/10.1007/s10552-012-9931-z.

[31] Blum A, Brand CU, Ellwanger U, Schlagenhauff B, Stroebel W, Rassner G, et al. Awareness and early detection of cutaneous melanoma: an analysis of factors related to delay in treatment. Br J Dermatol 1999;141(5):783–7. https://doi.org/10.1046/j.1365-2133.1999.03196.

[32] Jensen H, Tørring ML, Olesen F, Overgaard J, Vedsted P. Cancer suspicion in general practice, urgent referral and time to diagnosis: a population-based GP survey and registry study. BMC Cancer 2014;14:636. https://doi.org/10.1186/1471-2407-14-636.

[33] Richard MA, Grob JJ, Avril MF, Delaunay M, Gouvernet J, Wolkenstein P, et al. Delays in diagnosis and melanoma prognosis (I): the role of patients. Int J Cancer (Pred Oncol) 2000;89:271–9.

[34] Schmid-Wendtner MH, Baumert J, Stange J, Volkenandt M. Delay in the diagnosis of cutaneous melanoma: an analysis of 233 patients. Melanoma Res 2002;12(4):389–94. https://doi.org/10.1097/00008390-200208000-00012.