Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review

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Background: It is unclear whether more timely cancer diagnosis brings favourable outcomes, with much of the previous evidence, in some cancers, being equivocal. We set out to determine whether there is an association between time to diagnosis, treatment and clinical outcomes, across all cancers for symptomatic presentations.

Methods: Systematic review of the literature and narrative synthesis.

Results: We included 177 articles reporting 209 studies. These studies varied in study design, the time intervals assessed and the outcomes reported. Study quality was variable, with a small number of higher-quality studies. Heterogeneity precluded definitive findings. The cancers with more reports of an association between shorter times to diagnosis and more favourable outcomes were breast, colorectal, head and neck, testicular and melanoma.

Conclusions: This is the first review encompassing many cancer types, and we have demonstrated those cancers in which more evidence of an association between shorter times to diagnosis and more favourable outcomes exists, and where it is lacking. We believe that it is reasonable to assume that efforts to expedite the diagnosis of symptomatic cancer are likely to have benefits for patients in terms of improved survival, earlier-stage diagnosis and improved quality of life, although these benefits vary between cancers.

Symptomatic diagnosis of cancer is important and has been the subject of considerable innovation and intervention in recent years to achieve timelier and earlier-stage diagnosis (Emery et al., 2014); the English National Awareness and Early Diagnosis Initiative has made a major contribution to this effort (Richards and Hiom, 2009; Richards, 2009a). We know that patients value timely diagnostic workup, and that later stage at diagnosis is one of the contributory factors to poor cancer outcomes (Richards, 2009b). However, it is less clear whether more timely cancer diagnosis brings favourable outcomes. Systematic reviews in breast cancer reported that delays of 3–6 months were associated with lower survival (Richards et al., 1999), and in colorectal cancer it was
concluded that there were no associations between diagnostic delays and survival and stage (Ramos et al, 2007, 2008; Thompson et al, 2010). Other reviews have been published for gynaecological cancers (Menczer, 2000), bladder (Fahmy et al, 2006), testicular (Bell et al, 2006), lung (Jensen et al, 2002; Olsson et al, 2009), paediatric cancers (Brasme et al, 2012a, b) and head and neck cancers (Goy et al, 2009; Seoane et al, 2012), all with equivocal findings. No review to date has undertaken this work in a range of different cancer types.

Longer time to diagnosis may be detrimental in several ways: a more advanced stage at diagnosis, poorer survival, greater disease-related and treatment-related morbidity and adverse psychological adjustment. Conversely, harm may be caused by earlier detection of cancers without improving survival (lead-time), and detection of slow-growing tumours not needing treatment (over-diagnosis) (Esserman et al, 2013). A scoping review, undertaken before the review reported here, showed that observational studies in many cancers reported no association or an inverse relationship between longer diagnostic times and better outcomes (Neal, 2009). We therefore undertook a systematic review of the literature aiming to determine whether there is an association between time to diagnosis, treatment and clinical outcomes, across all cancers for symptomatic presentations only.

MATERIALS AND METHODS

We undertook a systematic review in two phases. The original review was conducted in 2008–10, and the literature from inception of databases to February 2010 was searched; the update was conducted in 2013–14, and the literature from February 2010 to November 2013 was searched. The original review did not include breast or colorectal cancer (because of prior systematic reviews); however, these were included in the update (as we knew of more papers published in these cancers). The review adhered to principles of good practice (Egger et al, 2001; NHS Centre for Reviews and Dissemination, 2001). Reporting is in line with the PRISMA recommendations (Moher et al, 2009).

A search strategy was developed for Medline (Figure 1) and adapted for other search sources. A range of bibliographic databases were searched for relevant studies. These were as follows:

- MEDLINE, MEDLINE in-process, EMBASE, CINAHL, PsychINFO
- Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, Health Technology Assessment Database, NHS Economic Evaluation database.

Reference lists of studies included in this and previous reviews were hand-searched for relevant studies.

One reviewer screened the titles and abstracts of all records for relevance, and assessed potentially relevant records for inclusion. A second reviewer checked the decisions; disagreements were resolved by discussion or, if necessary, by a third reviewer. A study or analysis was included in the review if it:

- Was available as full text in English.
- Characteristics of included studies: study aim, population, location, setting, definitions of time intervals, data collection methods used and outcome measures.
- Clinical outcomes: included the measure of association, associations of intervals with outcomes and reported interpretation.

1. Exp neoplasms/
2. (time adj4 diagnosis).ti,ab.
3. (time adj4 consult).ti,ab.
4. (time adj4 treat).ti,ab.
5. (time adj4 refer).ti,ab.
6. (time adj4 present).ti,ab.
7. (time adj4 interval).ti,ab.
8. (time adj4 theapol).ti,ab.
9. or/2–8
10. (delay$ adj4 diagnosis).ti,ab.
11. (delay$ adj4 consult).ti,ab.
12. (delay$ adj4 treat).ti,ab.
13. (delay$ adj4 refer).ti,ab.
14. (delay$ adj4 present).ti,ab.
15. (delay$ adj4 interval).ti,ab.
16. (delay$ adj4 theapol).ti,ab.
17. (delay$ adj4 seek).ti,ab.
18. (delay$ adj4 care).ti,ab.
19. (delay adj4 detect*).ti,ab.
20. or/10–19
21. (interval adj4 diagnosis).ti,ab.
22. (interval adj4 consult).ti,ab.
23. (interval adj4 treat).ti,ab.
24. (interval adj4 refer).ti,ab.
25. (interval adj4 present).ti,ab.
26. (interval adj4 theapol).ti,ab.
27. or/21–26
28. (late adj4 diagnosis).ti,ab.
29. (late adj4 detect*).ti,ab.
30. (late adj4 present).ti,ab.
31. or/28–30
32. (duration adj4 symptom).ti,ab.
33. Wat$h time$.mp.
34. 9 or 20 or 27 or 31 or 32 or 33
35. 1 and 34
36. limit 35 to (english language and humans and yn="2010 -current")
37. Editorial or letter or practice guideline or biography or case reports or clinical conference or comment or consensus development conference or NIH or guideline or newspaper article or patient education handout
38. Cells(Mesh) or Mass screening(Mesh) or genetic screening(Mesh) or pregnancy(Mesh)
39. Pharmaceutical preparations[Mesh]
40. Chemical. hw
41. #37 or #38 OR #39 or #40
42. 36 NOT 41

The original search strategy was found to be too sensitive and produced a large number of non-relevant references. This was revised and refined to capture all relevant articles. The number of databases searched was also more extensive for the original search, but on investigation, it was evident that all included articles had been found on databases subsequently chosen for the updated review.
Bias assessment: we envisaged at the outset that there would be considerable variation between included studies in terms of study design, and that many may be of poor quality (Neal, 2009). We therefore considered that the assessment of methodological quality was especially important. However, at that time, there were no widely accepted checklists for checking the quality of prognostic studies, and there was little empirical evidence to support the importance of individual criteria, or study features, in affecting the reliability of study findings (Altman, 2001). Hence, we decided against the use of quality scoring, and to use a checklist instead of a scale. Judgements on the risk of bias were made according to a number of domains, using a generic list of questions within each domain (Figure 2), based primarily on a framework for assessing prognostic studies (Altman, 2001). For the updated review, and being aware of more recent literature on assessing the quality of prognostic studies, we decided to keep

| Bias assessment tool. |
|-----------------------|
| **Sample representativeness:** Is the sample representative of the relevant cancer patient population? The population may be quite specific, typified by age, stage, ethnicity or other factors. |
| **Yes:** only if this is clearly reported |
| **Can’t tell:** if it’s reported in an ambiguous way |
| **Not reported:** if it doesn’t say |
| If none of the above, please qualify with free text (this may be a majority of studies) |
| **Characteristics reporting:** Was the reporting of participant characteristics complete? |
| **Yes:** only if this is clearly and fully reported |
| **Can’t tell:** is it’s reported in an ambiguous way |
| **Not reported:** if it doesn’t say |
| If none of the above, please qualify with free text (this may be the majority of studies, for example those who just give age and gender) |
| **Representativeness of participants:** Were participants who participated (or whose data were used) representative of the sample from which they (or it) were sourced? |
| **Yes:** only if this is clearly and fully reported |
| **Can’t tell:** is it’s reported in an ambiguous way |
| **Not reported:** if it doesn’t say |
| If none of the above, please qualify with free text |
| **Bias minimisation in measurement of symptom duration:** Were steps taken (as stated by the investigators) to minimise and check for, biases and inaccuracies introduced owing to the method used for measurement of symptom duration? |
| **Yes:** if clear evidence of this, please list information as free text: MANDATORY |
| **No:** if no evidence of this |
| **Can’t tell:** if unclear (this includes where results may be reported but no mention in methods) |
| **Independent variable assessment:** Was the assessment symptom duration (explanatory variable) conducted independent of the assessment of the outcome variable? |
| **Yes:** if reported as done |
| **No:** if clearly reported that same researcher did it |
| **Not reported:** if it doesn’t say |
| **Not applicable:** if the method does not require this to be done, for example, database study |
| **A priori definition of outcome variable:** Was the outcome variable specified/defined a priori? |
| **Yes** |
| **No** |
| **Appropriate definition of outcome variable:** Was the outcome variable clearly defined? |
| **Yes:** for example, type of stage, type of survival, not necessary to enter detail |
| **No:** anything other than yes |
| **Multivariate analysis:** Was multivariate analysis conducted? |
| **Yes** |
| **No** |
| **Prognostic adjustment:** Was adjustment for important prognostic factors conducted as part of the analysis? |
| **Yes:** if clear evidence of this, (for example: performance status, age, smoking, co morbidity), please qualify with free text MANDATORY |
| **No:** if no evidence of this |
| **Can’t tell:** if unclear (this includes where results may be reported but no mention in methods), please qualify with free text MANDATORY |
| **Outlier adjustment for symptom duration:** Was adjustment for outliers conducted as part of the analysis? |
| **Yes:** if clear evidence of this, please qualify with free text MANDATORY |
| **No:** if no evidence of this |
| **Not applicable:** for example if there were no symptom durations greater than 2 years or less for more quickly diagnosed cancers |
| **Can’t tell:** if unclear (this includes where results may be reported but no mention in methods), please qualify with free text MANDATORY |
| **Confounder adjustment:** Was adjustment for confounders (identified in advance of the study) conducted as part of the analysis? |
| **Yes:** if clear evidence of this, please qualify with free text MANDATORY |
| **No:** if no evidence of this |
| **Can’t tell:** if unclear (this includes where results may be reported but no mention in methods), please qualify with free text MANDATORY |

We also identified studies (update only 2010–13) that addressed the so-called ‘waiting time paradox’ (see text).
the original questions, as they were in line with the new Quality in Prognosis Studies tool (Hayden et al., 2006, 2013). In addition, in the update, we identified studies that addressed the so-called ‘waiting time paradox’ (Crawford et al., 2002), which were likely to be of higher analytical quality. These were defined as follows: ‘articles that undertake an analysis or sub-analysis that specifically includes or excludes patients who are either diagnosed very quickly (e.g., within 4–8 weeks, although this will vary between cancers), or have very poor outcomes (e.g., deaths within a short time after diagnosis, e.g., within 4–8 weeks).’ Agreement on inclusion in this subset of articles was done by two members of the study team. This is the ‘paradox’ caused by the inclusion of patients with aggressive disease who invariably present early and have poor outcomes as a result of the aggressive disease, and is a form of confounding by indication.

- Clinical outcomes: the measure of association, associations of time intervals.
- Quality of the studies (Supplementary Online Material).
- Bias assessment: the bias assessment demonstrates the mixed quality of the studies (Supplementary Online Material).

RESULTS

Study selection. The number of studies screened, assessed for eligibility, included and reasons for exclusion are shown in Table 1. The number of studies screened, assessed for inclusion because:

- not English language, not full text peer reviewed paper, opinion piece, no relevant outcome data, does not report at least one time interval to diagnosis or treatment, case reports, guidelines/methodology, not primary symptomatic cancer, study protocol, duration data not linked to outcome, review, (n = 852).
- Records rejected on the basis of title and/or abstract as not relevant to this review (n = 191376).
- Records identified for all cancer sites by electronic searching after de-duplication (n = 193 077).
- Records identified through other sources (searching bibliographies, reference lists of reviews) (n = 41).
- Records assessed for retrieval (n = 1742).
- Breast and colorectal cancer records published up to March 2010 (n = 706)*.
- Full-text articles retrieved for detailed evaluation and assessment for inclusion (n = 1036).
- Full-text articles excluded, with reasons:
  - not English language, not full text peer reviewed paper, opinion piece, no relevant outcome data, does not report at least one time interval to diagnosis or treatment, case reports, guidelines/methodology, not primary symptomatic cancer, study protocol, duration data not linked to outcome, review, (n = 852).

Figure 3. Flow diagram. *Of those breast and colorectal cancer records published up to March 2010 (n = 706) assessed for retrieval, 330 were retrieved and assessed for inclusion but were not included in the evaluation, as systematic reviews on these cancers had been recently published. The follow-up review, covering the period March 2010 to October 2013, included both breast and colorectal cancers in the qualitative synthesis.

Clinical and psychological outcomes. Data collection for the outcome measures was predominantly retrospective review of medical records (using a variety of the following: clinical, pathological, histological and imaging) and cancer registries. Patient questionnaires were used for studies with psychological outcomes. Most studies used various measures of survival (or mortality) and/or stage as outcome measures.

Bias assessment. The bias assessment demonstrates the mixed quality of the studies (Supplementary Online Material). On a positive note, the characteristics and representativeness of the samples were reported in most articles, the definitions and appropriateness of time intervals were well reported and many studies undertook multivariable analysis. However, the representativeness of the samples was not reported in many articles, and few studies undertook confounder adjustment, prognostic adjustment or attempted bias minimisation. Only seven of the articles made an attempt to address the waiting time paradox (Tørring et al., 2011, 2012, 2013; Brasme et al., 2012a, b; Elit et al., 2013; Gobbi et al., 2013; Pruitt et al., 2013). Hence, most studies failed to address the premise of confounding by indication—
that is, the relationship between the diagnostic pathway (and hence the time interval) and prognosis.

Study characteristics. Of the 177 articles included, there were a total of 401,760 participants, with a range of 13 to 147,682 in individual study size (Supplementary Online Material). There were 88 European studies with 23 from the UK, 9 from Italy, 8 from Spain, 8 from the Netherlands, 7 from Denmark, 7 from Finland, 5 from France, 5 from Norway, 3 from Switzerland, 3 from Sweden, 3 from Germany, 2 from Poland and 1 each from Austria, Belgium, Romania, Greece and joint UK/Denmark. There were 18 studies from Asia, with 5 from India, 4 from Japan, 4 from China, 2 from Hong Kong, 2 from Malaysia and 1 from South Korea. There were 59 studies from the Americas, with 47 studies from the USA, 8 from Canada and 4 from Brazil. In addition, there were three from Turkey, two from Israel, two from Australia, one each from New Zealand, Saudi Arabia, Libya, South Africa and one unspecified.

148 were based in specialist care 148 (106 single site, 38 multisite and 4 unspecified), 21 were population based, 3 were set in primary care, 3 database studies, 1 used hospital cancer registry data and 1 was unspecified. Study design varied hugely, and it included prospective and retrospective cohort studies, reviews of medical records, database analyses, patient surveys and interviews. The majority of the studies had retrospective designs.

Synthesis of main findings. The results of individual studies are presented in Supplementary Online Material. No meta-analyses were possible. The results are reported cancer by cancer. Studies are grouped under ‘children teenagers and young adults’ where they reported at least a significant proportion of participants aged <25 years. Summaries for each cancer are reported in Table 1. Studies that reported ‘positive’ associations (i.e., where there was evidence of shorter intervals being associated with more favourable outcomes) are presented first, followed by studies that reported no associations, followed by those that reported ‘negative’ associations (i.e., where there was evidence of shorter intervals being associated with less favourable outcomes). In each section, studies reporting survival outcomes (or mortality, but for simplicity just referred to as survival in the table) are presented before those reporting stage and other outcomes. A brief narrative for each cancer is provided below.

Figure 4. Definitions of time interval.
The association between diagnostic times and outcomes in cancer

For breast cancer, four studies reported positive associations, including one of the studies that addressed the waiting time paradox, and was able to demonstrate the effect of different diagnostic intervals on mortality (Tørring et al, 2013). The remainder reported no associations.

The lung studies had mixed findings, with similar numbers of studies reporting positive, negative and no associations, across a range of different time intervals. However, one of the studies reporting a positive association with mortality for diagnostic intervals addressed the waiting time paradox (Tørring et al, 2013). For colorectal cancer, although many studies reported no associations, more studies reported a positive, rather than a negative, association. Indeed, four studies addressing the waiting time paradox were included, three of which reported a positive association (Tørring et al, 2011, 2012, 2013) and one a negative association (Pruitt et al, 2013). Of the upper gastrointestinal cancers, most studies reported no association, and more reported a

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### Table 1. Summary results from narrative synthesis, by cancer

| Positive association                                      | No association                                      | Negative association                                      |
|----------------------------------------------------------|-----------------------------------------------------|----------------------------------------------------------|
| **Breast**                                               |                                                     |                                                          |
| Survival                                                |                                                     |                                                          |
| Diagnostic interval (Tørring et al, 2013)                | Survival                                            | Survival                                                |
| Treatment interval (Yun et al, 2012; Smith et al, 2013)  | Treatment interval (Brazda et al, 2010; McLaughlin et al, 2012; Eastman et al, 2013; Mujar et al, 2013; Redaniel et al, 2013; Sue et al, 2013) | Survival (Brazda et al, 2010; McLaughlin et al, 2012; Eastman et al, 2013; Mujar et al, 2013; Redaniel et al, 2013; Sue et al, 2013) |
| Stage                                                    |                                                     |                                                          |
| Symptom onset to diagnosis (Emniah et al, 2012; Wamer et al, 2012) | Stage                                               | Stage                                                   |
|                                                        | Treatment interval (Wright et al, 2010; Wagner et al, 2011) | Treatment interval (Wright et al, 2010; Wagner et al, 2011) |
|                                                        |                                                     |                                                          |
| **Lung**                                                 |                                                     |                                                          |
| Survival                                                |                                                     |                                                          |
| Diagnostic interval (Tørring et al, 2013)                | Survival                                            | Survival                                                |
| Symptom onset to diagnosis (Maguire et al, 1994)         | Symptom onset to treatment (Annakkaya et al, 2007)   | Treatment interval (Gonzalez-Barcala et al, 2010) |
|                                                        | Patient interval (Loh et al, 2006)                   |                                                        |
|                                                        | Diagnostic interval (Loh et al 2006; Pita-Fernandez et al, 2007; Skaug et al, 2011) |                                                        |
|                                                        | Treatment interval (Diaconescu et al, 2011; Yun et al, 2012) |                                                        |
|                                                        | Symptom onset to being seen in specialist care (Garcia-Barcala, 2012) |                                                        |
|                                                        |                                                     |                                                          |
| **Gastric**                                             |                                                     |                                                          |
| Survival                                                |                                                     |                                                          |
| Treatment interval (Yun et al, 2012)                     | Treatment interval (Maguire et al, 1994; Martin et al, 1997; Windham et al, 2002; Alvantakis et al, 2006) | Patient interval (Yilmaz et al, 2008; Tokuda et al, 2009) |
|                                                        | Patient interval (Lim et al, 1974)                   | Patient interval (Yilmaz et al, 2008; Tokuda et al, 2009) |
|                                                        | Primary care interval (Lim et al, 1974)               | Primary care interval (Lim et al, 1974)                  |
|                                                        |                                                     |                                                          |
| **Oesophageal**                                         |                                                     |                                                          |
| Stage                                                   |                                                     |                                                          |
| Symptom onset to diagnosis (Martin et al, 1997)          | Diagnostic interval (Fernandez et al, 2002)           | Diagnostic interval (Fernandez et al, 2002)               |
|                                                        | Patient interval (Tokuda et al, 2009)                 | Patient interval (Tokuda et al, 2009)                    |
|                                                        |                                                     |                                                          |
| **Gastro-oesophageal**                                  |                                                     |                                                          |
| Other outcomes                                          |                                                     |                                                          |
| Treatment interval and morbidity and in-hospital mortality (Grotenhuis et al, 2013) |                                                     |                                                          |
|                                                        |                                                     |                                                          |
| **Pancreatic**                                          |                                                     |                                                          |
| Survival                                                |                                                     |                                                          |
| Symptom onset to diagnosis (Gobbi et al, 2013)           | Survival                                            | Survival                                                |
| Symptom onset to referral (Raptis et al, 2010)           | Treatment interval (Yun et al, 2012)                 | Treatment interval (Yun et al, 2012)                    |
|                                                        | Stage                                               | Stage                                                   |
|                                                        | Patient interval (Tokuda et al, 2009)                 | Patient interval (Tokuda et al, 2009)                    |
|                                                        | Other outcomes                                      | Diagnostic interval and resectability (McLean et al, 2013) |
|                                                        |                                                     |                                                          |
Table 1. (Continued)

| Positive association | No association | Negative association |
|----------------------|---------------|----------------------|
| **Hepatocellular**   |               |                      |
| Survival             |               |                      |
| Treatment interval   |               |                      |
| (Singal et al, 2013) |               |                      |
| Stage                |               |                      |
| Patient interval     |               |                      |
| (Tokuda et al, 2009) |               |                      |
| **Colorectal**       |               |                      |
| Survival             |               |                      |
| Diagnostic interval  |               |                      |
| (Tørring et al, 2011, 2012, 2013) | | |
| Diagnosis to treatment | (O’Brien et al, 2011) | |
| Symptom onset to diagnosis | (Ware et al, 1980, Wishnow et al, 1990) | |
| Patient interval     |               |                      |
| (Tokuda et al, 2009) |               |                      |
| Referral interval    |               |                      |
| (Valentin-Lopez et al, 2012) | | |
| **Prostate**         |               |                      |
| Survival             |               |                      |
| Diagnostic interval  |               |                      |
| (Tørring et al, 2011, 2012, 2013) | | |
| Diagnosis to treatment | (Korets et al, 2012, Sun et al, 2012) | |
| Symptom onset to diagnosis | (Prout and Griffin, 1984, Medical Research Council Working Party, Testicular Tumours, 1985) | |
| Patient interval     |               |                      |
| (Neal et al, 2007)   |               |                      |
| **Testicular**       |               |                      |
| Survival             |               |                      |
| Patient interval     |               |                      |
| (Hanson et al, 1993) |               |                      |
| Symptom onset to treatment | (Prout and Griffin, 1984) | |
| (Huyghe et al, 2007, Moul et al, 1990-non-seminoma only) | | |
| Symptom onset to treatment | (Bosl et al, 1981, Moul et al, 1990, Huyghe et al, 2007-non-seminoma only) | |
| Patient interval     |               |                      |
| (Hanson et al, 1993) |               |                      |
| Other outcomes       |               |                      |
| Diagnostic interval  |               |                      |
| (Akdas et al, 1986)  |               |                      |
| Symptom onset to treatment | (Schern, 1983) | |
| **Renal**            |               |                      |
| Stage                |               |                      |
| Patient interval     |               |                      |
| (Tokuda et al, 2009) |               |                      |
| **Bladder**          |               |                      |
| Survival             |               |                      |
| Symptom onset to diagnosis | (Hollenbeck et al, 2010) | |
| Symptom onset to referral | (Wallace et al, 2002) | |
| Stage                |               |                      |
| Diagnostic interval  |               |                      |
| (Liedberg et al, 2003) |               |                      |
| **Upper tract urothelial carcinoma** | | |
| Stage                |               |                      |
| Diagnosis to treatment | (Waldert et al, 2010, Sundi et al, 2012) | |
| **Cervical**         |               |                      |
| Stage                |               |                      |
| Patient interval     |               |                      |
| (Fruchter and Boyce, 1981) | | |
| **Other outcomes**   |               |                      |
| Patient interval and chance of complete remission | (Akdas et al, 1986) | |
| and response to treatment | (Schern, 1983) | |
The association between diagnostic times and outcomes in cancer

| Table 1. (Continued) | Endometrial | Ovarian | Head and neck | Brain/CNS | Melanoma | Non-melanoma skin |
|-----------------------|-------------|---------|---------------|-----------|-----------|------------------|
| **Endometrial**       |             |         |               |           |           |                  |
| **Stage**             |             |         |               |           | Survival  | Survival          |
| Symptom onset to diagnosis (Fruchter and Boyce, 1981; Franceschi et al, 1983; Obermaier et al, 1996) | Survival | Symptom onset to diagnosis (Menczer et al, 1995) | Survival | Referral to treatment (Crawford et al, 2002) |
| Other outcomes        |             |         |               |           | Survival  | Diagnosis to treatment (Elit et al, 2013) |
| Symptom onset to treatment and quality of life and satisfaction (Robinson et al, 2012) | Survival | Symptom onset to diagnosis (Pitchers and Martin, 2006–oral and pharyngeal cancer (separately); Al-Rajhi et al, 2009–nasopharyngeal) | Survival | Symptom onset to diagnosis (Lurie et al, 2010) |
| **Ovarian**           |             |         |               |           | Survival  | Survival          |
| Symptom onset to diagnosis (Nagle et al, 2011) | Survival | Symptom onset to diagnosis (Nagle et al, 2011) | Survival | Symptom onset to treatment (Caudell et al, 2011–head and neck unspecified; Brouha et al, 2000–laryngeal) |
| Other outcomes        |             |         |               |           | Survival  | Survival          |
| Symptom onset to treatment (Hansen et al, 2004–laryngeal) | Survival | Symptom onset to diagnosis (Vernham and Crowther, 1994 head and neck unspecified) | Survival | Symptom onset to treatment (McGurk et al, 2005–head and neck unspecified) |
| **Head and neck**     |             |         |               |           | Survival  | Survival          |
| Survival              |             |         |               |           | Survival  | Survival          |
| Patient interval (Koivunen et al, 2001–pharyngeal; Teppo and Alho, 2008–pharyngeal and laryngeal cancers (separately); Diagnostic interval (Alho et al, 2006–head and neck unspecified; Teppo et al, 2003–laryngeal; Teppo and Alho, 2008–laryngeal) Symptom onset to treatment (Hansen et al, 2004–laryngeal) Treatment interval (Sidler et al, 2010–nasopharyngeal) | Survival | Patient interval (Teppo et al, 2003–laryngeal; Teppo and Alho, 2008–tongue) Diagnostic interval (Seoane et al, 2010–oral; Teppo and Alho, 2008–pharyngeal and tongue (separately); Koivunen et al, 2001–laryngeal) Symptom onset to treatment (McGurk et al, 2005–head and neck unspecified) | Survival | Patient interval (Allison et al, 1998–upper aerodigestive tract; Al-Rajhi et al, 2009–nasopharyngeal; Brouha et al, 2005a–laryngeal cancer; Wildt et al, 1995–oral; Teppo et al, 2009–vestibular schwannoma) Diagnostic interval (Teppo et al, 2009–vestibular schwannoma; Ho et al, 2004–oropharyngeal) Symptom onset to diagnosis (Mizara et al, 1998–laryngeal; Scott et al, 2005–oral) | Survival | Symptom onset to referral (Vernham and Crowther, 1994 head and neck unspecified) |
| Stage                 |             |         |               |           | Survival  | Survival          |
| Patient interval (Kumar et al, 2001–oral; Brouha et al, 2005b–oral and pharyngeal cancer (separately); Lee et al, 1997–nasopharyngeal; Sheng et al, 2008–nasopharyngeal; Tromp et al, 2005–head and neck unspecified; Tokuda et al, 2009–head and neck unspecified; Tromp et al, 2005–head and neck unspecified) Diagnostic interval (Allison et al, 1998–aerodigestive tract; Al-Rajhi et al, 2009–nasopharyngeal Symptom onset to diagnosis (Allison et al, 1998–aerodigestive tract; Al-Rajhi et al, 2009–nasopharyngeal) Symptom onset to referral (Pitchers and Martin, 2006–oropharyngeal) | Survival | Patient interval (Teppo et al, 2003–laryngeal; Teppo and Alho, 2008–tongue) Diagnostic interval (Seoane et al, 2010–oral; Teppo and Alho, 2008–pharyngeal and tongue (separately); Koivunen et al, 2001–laryngeal) Symptom onset to treatment (McGurk et al, 2005–head and neck unspecified) | Survival | Symptom onset to referral (Vernham and Crowther, 1994 head and neck unspecified) |
| Other outcomes        |             |         |               |           | Survival  | Survival          |
| Symptom onset to diagnosis (Allison et al, 1998–aerodigestive tract; Al-Rajhi et al, 2009–nasopharyngeal) Symptom onset to referral (Pitchers and Martin, 2006–oropharyngeal) | Survival | Patient interval (Teppo et al, 2003–laryngeal; Teppo and Alho, 2008–tongue) Diagnostic interval (Seoane et al, 2010–oral; Teppo and Alho, 2008–pharyngeal and tongue (separately); Koivunen et al, 2001–laryngeal) Symptom onset to treatment (McGurk et al, 2005–head and neck unspecified) | Survival | Symptom onset to referral (Vernham and Crowther, 1994 head and neck unspecified) |
| **Brain/CNS**         |             |         |               |           | Survival  | Survival          |
| Other outcomes        |             |         |               |           | Survival  | Survival          |
| Symptom onset to diagnosis and progressive neurological deterioration (Balasa et al, 2012) | Survival | Patient interval (Teppo et al, 2003–laryngeal; Teppo and Alho, 2008–tongue) Diagnostic interval (Seoane et al, 2010–oral; Teppo and Alho, 2008–pharyngeal and tongue (separately); Koivunen et al, 2001–laryngeal) Symptom onset to treatment (McGurk et al, 2005–head and neck unspecified) | Survival | Symptom onset to referral (Vernham and Crowther, 1994 head and neck unspecified) |
| **Melanoma**          |             |         |               |           | Survival  | Survival          |
| Survival              |             |         |               |           | Survival  | Survival          |
| Patient interval (Temoshok et al, 1984, Montella et al, 2002) Diagnostic interval (Temoshok et al, 1984; Metzger et al, 1998, Montella et al, 2002; Terring et al, 2013) | Survival | Patient interval (Cassileth et al, 1982, Schmid-Wendtner et al, 2002; Carli et al, 2003; Baade et al, 2006) Diagnostic interval (Cassileth et al, 1982, Schmid-Wendtner et al, 2002; Baade et al, 2006) Symptom onset to diagnosis (Krige et al, 1991; Baade et al, 2006) | Survival | Symptom onset to treatment (Cassileth et al, 1982, Schmid-Wendtner et al, 2002; Carli et al, 2003; Baade et al, 2006) |
| Stage                 |             |         |               |           | Survival  | Survival          |
| Patient interval (Richards et al, 1999) Symptom onset to diagnosis (Helsing et al, 1997) | Survival | Patient interval (Cassileth et al, 1982, Schmid-Wendtner et al, 2002; Carli et al, 2003; Baade et al, 2006) Diagnostic interval (Cassileth et al, 1982, Schmid-Wendtner et al, 2002; Baade et al, 2006) Symptom onset to diagnosis (Krige et al, 1991; Baade et al, 2006) | Survival | Symptom onset to treatment (Cassileth et al, 1982, Schmid-Wendtner et al, 2002; Carli et al, 2003; Baade et al, 2006) |
| **Non-melanoma skin** |             |         |               |           | Survival  | Survival          |
| Stage                 |             |         |               |           | Survival  | Survival          |
| Patient interval (Tokuda et al, 2009) | Survival | Patient interval (Cassileth et al, 1982, Schmid-Wendtner et al, 2002; Carli et al, 2003; Baade et al, 2006) Diagnostic interval (Cassileth et al, 1982, Schmid-Wendtner et al, 2002; Baade et al, 2006) Symptom onset to diagnosis (Krige et al, 1991; Baade et al, 2006) | Survival | Symptom onset to treatment and larger lesions (Renzì et al, 2010) |
| Other outcomes        |             |         |               |           | Survival  | Survival          |
| Symptom onset and presentation to specialist care and increase in tumour size (Alam et al, 2011) | Survival | Patient interval (Cassileth et al, 1982, Schmid-Wendtner et al, 2002; Carli et al, 2003; Baade et al, 2006) Diagnostic interval (Cassileth et al, 1982, Schmid-Wendtner et al, 2002; Baade et al, 2006) Symptom onset to diagnosis (Krige et al, 1991; Baade et al, 2006) | Survival | Symptom onset to treatment and larger lesions (Renzì et al, 2010) |
negative, rather than a positive, association. For pancreatic cancer, two of the five studies reported a positive association, one of which addressed the waiting time paradox (Gobbi et al., 2013). The other three studies reported no association.

Two of the prostate studies reported a positive association for survival/mortality, one of which addressed the waiting time paradox (Tørring et al., 2013); the others reported no association. Two of the bladder studies reported a positive association; the others reported no association. For testicular cancer, 15 studies reported positive associations, and the remainder had no associations.

For gynaecological cancers, of the four studies examining cervix, one reported a positive association; the others reported no association. For endometrial and ovarian cancers, there were similar numbers of studies with positive, negative and no associations. One of the endometrial studies that reported a negative association addressed the waiting time paradox (Elit et al., 2013).

### Table 1. (Continued)

| Positive association | No association | Negative association |
|----------------------|----------------|---------------------|
| **CTYA** | | |
| **Survival** | Symptom onset to diagnosis (Marwaha et al, 2010b-leukaemia; Ferrai et al, 2010-soft tissue sarcomas) | Symptom onset to diagnosis (Kameda-Smith et al, 2013-soft tissue sarcomas; Sethii et al, 2013-posterior fossa tumours) | Patient interval (Kükal et al, 2009-brain tumours) |
| | First seen in specialist care to diagnosis (Marwaha et al, 2010a-leukaemia) | Diagnostic interval (Lins et al, 2012-leukaemia; Crawford et al, 2009-primary spinal cord tumours) | First symptom to treatment (Erwenne and Franco, 1989-retinoblastoma) |
| **Stage** | Diagnostic interval (Wallach et al, 2006-retinoblastoma) | Patient interval (Yang et al, 2009-osteosarcoma; Simpson et al, 2005-Ewing’s sarcoma) | Diagnostic interval (Crawford et al, 2009-primary spinal cord tumours; Halperin et al, 2001-Ewing’s sarcoma) |
| **Other outcomes** | Symptom onset to treatment and extra-ocular disease (Erwenne and Franco, 1989-retinoblastoma) | Symptom onset to diagnosis and eye loss (Butros et al, 2002-retinoblastoma) | Treatment interval and relapse rate (Wahl et al, 2012-leukaemia) |
| **Leukaemia** | | | |
| **Survival** | Diagnostic interval (Friese et al, 2011 (chronic lymphocytic); Symptom onset to diagnosis (Prabhu et al, 1986 (chronic myeloid)) | Treatment interval (Bertoli et al, 2013 (acute myeloid)) | |
| **Lymphoma** | | | |
| **Survival** | Symptom onset to diagnosis (Jacobi et al, 2008 (fOLLlicular); Maguire et al, 1994 (unspecified); Norum, 1995 (Hodgkin’s)) | Symptom onset to diagnosis (Kim et al, 1995; Foulc et al, 2003 (both Sezary syndrome)) | |
| **Myeloma** | | | |
| **Survival** | Symptom onset to diagnosis (Kariyawasan et al, 2007) | | Symptom onset to diagnosis (Kariyawasan et al, 2007; Friese et al, 2009) |
| **Other outcomes** | Symptom onset to diagnosis and complications at diagnosis (Kariyawasan et al, 2007; Friese et al, 2009) | | |
| **Connective tissue** | | | |
| **Survival** | Symptom onset to treatment (Ruka et al, 1988 (soft tissue sarcoma); Symptom onset to diagnosis (Saritha et al, 2008 (soft tissue sarcoma); Symptom onset to diagnosis (Nakamura et al, 2011 (soft tissue sarcoma)) | Symptom onset to diagnosis (Rougriaff et al, 2007 (soft tissue sarcoma); Wurtz et al, 1999 (osteosarcoma) | |
| **Stage** | Symptom onset to diagnosis (Bacci et al, 2002 (osteosarcoma)) | Symptom onset to diagnosis (Toth-Fejel and Pommier, 2004) | |
| **Carcinoid** | | | |
| **Survival** | Symptom onset to diagnosis (Toth-Fejel and Pommier, 2004) | | |
| **Thyroid** | | | |
| **Stage** | Patient interval (Tokuda et al, 2009) | | |
| **Multisite** | | | |
| **Survival** | Diagnostic interval (Tørring et al, 2013 (breast, lung, colorectal, prostate and melanoma combined) | | |
For head and neck cancers (pharyngeal, laryngeal, oral and others), there were a large number of studies and these were equally divided between those reporting a positive association and those reporting no association. No studies reported a negative association.

For melanoma, eight studies reported positive associations, one of which addressed the waiting time paradox (Tørring et al, 2013); the remainder reported no associations. For non-melanoma skin, two studies reported positive associations and one reported no association.

There were a large number of studies covering the various cancers in children, teenagers and young adults. The findings of these were very mixed, with the biggest group showing no associations, and smaller but similar number of studies reporting both positive and negative associations. One of the ‘no association’ studies addressed the waiting time paradox (Brasme et al, 2012a, b).

For lymphoma, three studies reported no association or a negative association. For leukaemia, the three studies reported no associations. There were only two studies in myeloma, although both of these reported positive outcomes. For the various connective tissue cancers, three studies each reported a positive association and no association. The other cancer groups (brain/central nervous system, carcinoid, hepatocellular, renal, thyroid, upper tract urothelial carcinoma and multisite) only had one or two included studies.

**DISCUSSION**

**Summary of main findings.** This review is unique in that it has assessed the literature for a range of different cancer types, and hence we are able to make recommendations for policy practice and research that are not limited to one cancer (or group of cancers). The number of included studies in this review has shown the importance of this question to patients, clinicians and researchers. However, even within specific cancer types, there is only moderate consensus as to the nature of any associations between various time intervals in the diagnostic process and clinical outcomes, with some studies showing no associations, some studies showing better outcomes with shorter time intervals and some the opposite. There are more reports of an association between times to diagnosis and outcomes for breast, colorectal, head and neck, testicular and melanoma, with reports from a smaller number of studies for pancreatic, prostate and bladder cancers. The time intervals in the studies varied, making it impossible to draw consensus as to which intervals may be more, or less, important. Moreover, the methodological quality of many of these papers is mixed, despite a recent consensus paper on design and reporting of such studies (Weller et al, 2012). There is some evidence from papers published more recently that address the waiting time paradox in their analyses (Tørring et al, 2011, 2012, 2013; Brasme et al, 2012a, b; Elit et al, 2013, Gobbi et al, 2013, Pruitt et al, 2013), with most, but not all, of these reporting longer intervals being associated with poorer outcomes, particularly mortality. This is important and begins to provide more robust evidence about the relationship between time to diagnosis and outcomes.

**Findings within the context of the literature.** The previous cancer-specific reviews (Menczer, 2000; Jensen et al, 2002; Bell et al, 2006; Fahmy et al, 2006; Ramos et al, 2007, 2008; Goy et al, 2009; Olsson et al, 2009; Thompson et al, 2010; Brasme et al, 2012a, b), with the exception of the breast cancer (Richards et al, 1999), and to a lesser extent head and neck (Seoane et al, 2012), have been largely equivocal, probably because of the poor quality of the included studies. Our findings are largely in keeping with these reviews, although we have provided much more evidence than previous reviews for testicular cancer (Bell et al, 2006) and head and neck cancers (Goy et al, 2009). We have also identified more recent and probably high-quality papers providing better evidence for colorectal cancer than covered in previous reviews (Ramos et al, 2007, 2008; Thompson et al, 2010). We provide review findings for the first time for many cancers. We are also aware of further articles being published since the end date of our review. For example, one of these replicated the methods of one of the papers in our review (Tørring et al, 2011) on a sample of 958 colorectal cancers in Scotland, and reported that longer diagnostic intervals did not adversely affect cancer outcomes (Murchie et al, 2014). Another has reported that time to diagnosis in 436 Ewing tumours in France was not associated with metastasis, surgical outcome or survival (Brasme et al, 2014). One of our main findings, of the poor quality of reporting of time to diagnosis studies, replicates the findings of a recent paediatric systematic review (Launay et al, 2013).

**Strengths and weaknesses.** This is the largest and most comprehensive review in this field, and the first ‘all-cancer’ systematic review. The huge heterogeneity in both the outcomes and the time intervals used, within each cancer site, precluded meta-analyses. Another systematic review has recently reported similar difficulty in comparisons between studies (Lethaby et al, 2013). As previously stated, the review only contains studies in colorectal and breast cancer for 2010–13, and only these studies identified during the second round of searches were assessed to determine whether their analyses addressed the waiting time paradox. Survival, or mortality, is the most objective outcomes for these studies. However, many of the included studies in the review reported stage, or some other proxy. This may explain why stage and survival outcomes differ. Stage categorisation also varied, and some of the studies may be affected by post-hoc upstaging. A further problem with the literature is that of confounding by indication. Symptoms of more advanced cancer are likely to present differently and be investigated more promptly, as are patients presenting with so-called ‘red-flag’ symptoms. We were unable to assess for publication bias; indeed, if there was any publication bias, we cannot predict in which direction this would act.

**Implications for policy, practice and research.** Our main conclusion from this review is that we believe that it is reasonable to assume that efforts to expedite the diagnosis of symptomatic cancer are likely to have benefits for patients in terms of earlier-stage diagnosis, improved survival and improved quality of life. The amount of benefit varies between cancers; at present, there is more evidence for breast, colorectal, head and neck, testicular and melanoma, with evidence from a smaller number of studies for pancreatic, prostate and bladder cancers. There is either insufficient evidence or equivocal findings in the other cancers. The findings need replicating in using similar analytical methods, ideally also to address how much of a difference expedited diagnosis of different cancers would make on outcomes, and at which points in the diagnostic journey matters most. Until we have well-designed and well-analysed prospective studies to answer this question, it is difficult to determine the likely effect of interventions to reduce patient and diagnostic intervals on outcomes. This knowledge would inform the development of targeted intervention studies, to improve outcomes.

Hence, we recommend that policy, and clinicians, should continue the current emphasis on expediting symptomatic diagnosis, at least for most cancers. This can be achieved by clinicians having a high index of suspicion of cancer, the use of diagnostic technologies and rapid access to diagnostic investigations and fast-track pathways for assessment (Rubin et al, 2014). Finally, we recommend the need for more high-quality research in
Box 1. Key quality criteria for studies that examine the relationship between time intervals in cancer diagnosis and outcomes.

Good studies will report the definition of intervals in compliance with definitions in the Aarhus statement (Weller et al, 2012). The most common intervals reported are as follows:

- Patient interval – the time from when bodily changes and/or first symptoms are noticed to presentation of this change or symptom to a health care professional
- Diagnostic interval – the date from first presentation to a health care professional to diagnosis
- Referral interval – the date from referral to specialist care to being seen in specialist care

Good studies will report key dates in the diagnostic journey in a standardised way, with a full description. This includes, for example, the following:

- Dates when patients first notices bodily changes or symptoms and when they decide to seek help
- Date of first presentation of potential cancer symptom – including how such symptoms were defined
- Date of diagnosis – clear reporting of how this date was obtained and what date it actually represents (e.g., date of tissue diagnosis, date when patient informed)
- Dates of referral / investigation – including definitions of which were included and why

Good studies will fully describe appropriate data collection methods for time intervals. These will vary by interval, and different approaches to data collection (e.g., interviews, questionnaires, medical records, database studies) will give different answers. Data collection from patients is preferred for studies measuring patient intervals. Precise details regarding data collection methods are preferred. Good studies will fully describe and justify outcome measures. Mortality or survival is preferred, but some measure of stage (or other measure of disease severity or treatment modality) is also a useful endpoint. Studies capturing patient experience and quality of life and psychological outcomes are also needed.

Good studies will use a design that addresses bias and confounding (including confounding by indication); this includes measures to address the waiting time paradox.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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