WHICH INTERVAL IS MOST CRUCIAL TO PRESENTATION AND SURVIVAL IN GASTROESOPHAGEAL CANCER: A SYSTEMATIC REVIEW.

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ABSTRACT

Aim

To identify the most crucial interval to encourage earlier diagnosis in with gastroesophageal cancer and to identify potential factors effecting this interval.

Background

Gastroesophageal malignancy is the eighth most commonly presenting cancer with one of the worst survival rates. Identifying the most crucial period for intervention to inform earlier diagnosis is an important step towards improving survival.

Design

Mixed methods literature review.

Data Sources

CINAHL, MEDLINE and Academic search primer online databases were searched using keywords and inclusion/exclusion criteria. Empirical evidence published between 2000- 2016 with a focus on gastroesophageal cancer presentation and survival was reviewed to inform this study.

Review methods

Twelve studies were extracted for further review. Selected studies were appraised and presented through Olensen's 'delay interval' framework to inform the most crucial interval to survival in GOC.

Results

The findings identify the patient interval as the most critical period for encouraging earlier presentation and reducing advanced stage presentation in gastroesophageal cancer. The article

also highlighted some methodological limitations to cancer research, such as a lack of consensus in definitions which prevent statistical meta-analysis of cancer data, survivor bias in gastroesophageal cancer studies and a significant lack of qualitative evidence to reveal patient experience in presenting with this cancer.

Conclusion

Further research into the patient interval is required to elicit information on how and why patients present with their cancer symptoms.

Keywords

cancer, interval delay, oesophagogastric cancer, cancer data, advanced presentation, late presentation, literature review methodology, cancer methodology, GOC, early presentation

Summary statement

Why is this review required?

Internationally, there is a wide variety in presentation and survival in gastroesophageal cancer. This paper reviews evidence from several countries on presentation and survival, to identify the most crucial stage for intervention. It exposes the diverse range of timelines and nomenclature commonly used and reveals how these can affect findings in gastroesophageal cancer research. This paper presents these findings so that nurses can make informed decisions to deliver more targeted clinical interventions in the drive to encourage earlier diagnosis.

What are the key findings?

- This is the first study to reveal patient interval as the most crucial stage to survival in gastroesophageal cancer
- The incidence of gastroesophageal cancer is increasing but compared with other cancers, it is relatively overlooked.
- There is significant variation in how cancer survival and presentation is analysed and assessed. The disparate nomenclature needs closer review to ascertain meaningful results.

How should findings be used to influence policy/practice/research/education?

- Further evidence is required on patient level factors affecting presentation.
- Potential cancer patients need to be encouraged to seek treatment earlier.
- There is a need to standardise timeframes and definitions in early diagnosis cancer research.

Introduction

Gastroesophageal cancer (GOC) is a common cancer with a high morbidity and mortality rate. This systematic literature review of empirical evidence presents a narrative synthesis of evidence to identify the most crucial stage to encouraging earlier diagnosis. It also discusses the methodological limitations in cancer research. The findings are relevant to any cancer because earlier diagnosis is essential to survival. Knowing which interval is key in improved survival can guide further research and a more targeted clinical intervention.

Background

Gastroesophageal cancer (GOC) has an extremely high mortality and very low predicted survival rate following diagnosis (Adair *et al*., 2011; Allum *et al*., 2002; NHS 2008; Nuting *et al*., 2008; Office for National Statistics, 2005; Orengo *et al*., 2006; Sloggett *et al*., 2007; Zheng *et al*., 2010; Medical research Council, 2002; National Institute for Health and Clinical Excellence, 2005). GOC patients often present at an advanced stage, meaning tumours are infiltrated to such an extent that surgical cure is not possible. A recent meta-analysis of literature identified that an increased time to diagnosis is highly associated with a poor outcome and that advanced stage presentation is a major concern in many cancers (Neal *et al*., 2015)

Given the recently published guidelines seeking to clarify the range of definitions and timescales applied in early cancer research (Weller et al, 2012), a structured analysis of literature related to advanced presentation GOC is both timely and appropriate. This is the first systematic literature review specifically to focus on advanced stage GOC since the publication of Weller et al's (2012) 'Aarhus checklist'. The Aarhus checklist offers a tool to address the lack of consistency in definitions applied in early cancer diagnosis research. It is applied in this narrative synthesis of evidence as an adjunct to CASP for quality appraisal.

The Review

Aim

The aim of this review was to identify the most crucial interval for earlier diagnosis interventions and to identify common factors linked with advanced presentation. Objectives of this study were to:

- Undertake critical evaluation of all evidence evaluating presentation stage and survival in GOC.
- Present a narrative synthesis of evidence through Olenssen's 'delay interval framework'.
- Use the main characteristics and attributes linked with the delay periods to make recommendations for further study into early diagnosis.

Design

The York Centre for Reviews and Dissemination guidelines handbook (2009) was used to underpin a mixed method systematic review. Results of the initial search were structured using the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement. The most recent (2015) PRISMA guidance was adopted (Liberati et al., 2009; Moher, Liberati, Tetzlaff, & Altman, 2009; Moher et al., 2015; Shamseer et al., 2015). PRISMA is an effective and widely accepted tool in the standardisation of the information retrieval processes (Moher et al., 2015). For quality appraisal, relevant tools were taken from the Critical Appraisal Skills Programme (CASP), adapted to incorporate the Aarhus checklist for early diagnosis research. As there is a distinct lack of consensus in definitions of diagnosis and staging in the literature, results are presented as a narrative synthesis, through Olenssen's delay interval framework (Figure 1).

Search methods

A systematic literature search was undertaken for any papers published from 2000 - 2014 available through CINAHL, Medline, Psychinfo, EBSCOHOST and Academic Search Primer. This date range built on evidence available following Macdonald's seminal systematic review on upper gastrointestinal cancers in 2006 (Macdonald *et al*., 2006). The UK clinical research network had two relevant studies in progress, but no published results to date. The National Research Register and NIHR clinical trials gateway revealed no current trials on advanced stage presentations in cancers. Discussions with Cancer Research Charities UK and the Cancer Research (gastroesophageal group) network identified only one study protocol at an initial phase, so no results were available. Referenced citations were reviewed and followed up to identify any further studies of significance to this methodology.

Eligibility and study selection

Several frameworks exist to assist the process of structuring a research question (PICOs and PICo (JBI, 2014), MIP (Stretch et al, 2008) and SPIDER (Cooke, 2012). As the aim of this review was to identify the most crucial stage for interventions to encourage earlier presentation with GOC, PICo was used (Figure 2) to identify population, phenomena of interest and the context where the phenomena occurred (JBI, 2014). The research question was

Which interval is most crucial to encourage earlier presentation and improved survival in gastroesophageal cancer?

Explicit inclusion and exclusion criteria supported retrieval of relevant studies. Defining the population as all patients with a histological confirmation of gastroesophageal cancers provided a strict exclusion criteria. The phenomena of interest were any factors which had an impact on patient survival outcomes. Therefore, any studies which included patient doctor or service level interventions, survival analysis and, or revealing potential delays in the diagnostic journey were included. Studies without specific GOC focus were omitted from this review.

Studies conducted in any country were included, which were published in the English language. Dates were limited to studies published after 2000 only to maintain clinical and temporal relevance commensurate with improvements in care and treatments. Papers not meeting initial methodological scrutiny were discussed with co-authors. These were rejected through consensus opinion.

A Boolean search strategy of CINAHL, MEDLINE and Academic search primer yielded 12 papers. Synonyms and specific expressions for this were drawn from an initial scoping database review. MeSH terms are identified online (table 1) (available online via http address). Only empirical studies from peer reviewed scholarly journals were selected.

Data abstraction

The search strategy is presented in the PRISMA flow diagram (Figure 3). All papers focusing on treatment modalities or that were not GOC specific were rejected. After duplicates were removed, abstracts were reviewed. Those meeting inclusion criteria and addressing the research question were chosen for further analysis. Of these 24, a total of 15 empirical papers were selected for critique based on methodological rigour, appropriateness to the research question and definition of timescales. One audit detailing GOC incidence in the UK was appropriate to the review.

In general, most studies were retrospective reviews of cancer registry data (survival studies), or single centre cohort studies. The national registry data studies focused on events, survival and times and had large datasets (overall n = 26445 mean = 6611; median = 1507). The single centre cohort studies sought to explore factors which may be associated with any delays but relied on smaller numbers (n=48-491). There were two previous systematic reviews and a GP audit which either merged GOC with other cancers, or focused on factors associated with delay which were relevant to the discussion.

Quality Appraisal

This study included mainly cohort studies and papers on survival outcomes, so the appropriate CASP tool was applied to appraise results. Crowe and Sheppard (2011) have highlighted problems with having to access a range of different tools to appraise evidence on a single research question. They highlighted a need to apply a rigorous approach to appraising quality of evidence. Though the CASP tool for cohort studies encourages analysis of validity, results and local application, it is a generalised tool. Therefore, the Aarhus checklist was also applied to supplement and score papers under review. Using this checklist, scores were applied to how researchers had defined time points and intervals and which measurement and analytical tools had been used to underpin the research. These were found to vary significantly throughout the presented evidence. An online table (2) identifies how quality appraisal was applied to each study (http//www.) and an additional table (3) presents information on the appraisal outcome for each domain.

All papers were initially assessed by the primary researcher and results agreed through consensus opinion between co-authors who consisted of a professor of nursing and a gastroenterology medical specialist. Where two researchers disagreed, the third was consulted and the evidence discussed until consensus was reached.

Data synthesis

Results were conceptually mapped to Olennsen's delay intervals. This was used to identify the most crucial period for study into early diagnosis. This theoretical approach allows data to be presented through pre-determined themes which are drawn from the studies which have been selected (Braun and Clarke, 2006; Dixon-Woods *et al*, 2006). Results of the multiple studies were assimilated into a data extraction form which incorporated both CASP and Aarhus checklist components.

RESULTS

A total of 3839 records was extracted and narrowed following initial abstract review to 25 full length papers which were assessed for eligibility (Figure 1). From these 25 full text reviews, 12 papers were chosen for further analysis and quality appraisal. The search strategy revealed a significant lack of available evidence with sole focus on gastroesophageal cancer and delays in the diagnostic journey. Much of the research evaluated efficacy of treatment or survival outcomes but did not apportion the specific time of delay. Table 3 presents a summary of studies included alongside their quality appraisal results.

Studies which cover the total delay interval

Six studies presented in this review presented findings across all the delay intervals. Bus et al (2013) presented a study on 1, 3 and 5-year survival in GOC, from which factors relating to presentation may be drawn. Their data analysis reflected Coupland et al's (2012) methodology of retrospective analysis of cancer registry data. Bus et al (2013) revealed patients presenting with limited lymph node involvement had improved survival outcomes. They also revealed gender and absence of comorbidities was linked with increased survival. Numbers of subjects within the 1, 3 and 5 year cohorts were 703, 551 and 436 respectively, so the study was large. As with the UK, cancer notification is mandatory in the Netherlands, so there were no omissions from the dataset. The study relied on older data for survival analysis (some of these

data were 24 years old at the time of publication) and this can only reflect the treatments available at that time. However, the study showed the ability to treat with curative intent increased survival significantly. Presentation at later stages and with comorbidities significantly reduced survival outcomes. Advancing age was not linked with impaired survival for those in the three year and the 5-year groups, but it was significant in those people dying before 1 year. They did not undertake further analysis with histological subtypes, but found a wide disparity in survival between different treatments (surgery, neoadjuvant therapy) and the extent of tumour infiltration and lymph node involvement at presentation, concluding that the earlier patients present with their GOC, the more likely they are to survive.

Coupland et al's (2012) research focussed on GOC diagnosis across the UK. A sample of 13,3804 GOC diagnosed patients between 1998 - 2007 were analysed in relation to presentation and survival. This study revealed over half of middle and upper GOC were in females. This contradicts the usual 3:2 ratio of male to female GOC which is prevalent in the mainstay of GOC literature. The study also highlighted differences in survival relating to age, socioeconomic deprivation and stage of disease and called for further research into these factors. The authors conclude that early diagnosis is crucial to survival and encourage further studies to encourage earlier presentation, referrals and treatment.

In the US, cancer registry data are handled differently. Hence more reliance on single centre studies, or state led studies which focus on private or public held datasets. A single centre study in the United States of America by Hashemi et al's (2009) compared age groups and survival in 242 patients presenting between 1994 and 2004. They found younger patients tended to have higher lymphatic spread, but similar survival outcomes. Advanced stage presenters had worse outcomes, suggesting that the patient interval is crucial to survival.

Another Netherlands study – this time by Groentihaus et al. (2010) revealed the impact of pre hospital and hospital delays on survival. They identified that late onset of symptoms often predisposes a delay in presentation, but this study also identified a shorter gap from diagnosis to treatment significantly improved survival outcomes. The recommendations from this single centre cohort study of 491 patients presenting between the years 1991 and 2007 were on reduction of patient and hospital delays and expedition of treatment.

In Malaysia, Abdullah et al (2010) studied 143 patients presenting between 1998 and 2003, identified most patients in Malaysia present at very advanced stages and had very low survival outcomes. They also found a strong incidence in those from lower socioeconomic groups. This study was limited through its geography and over 71% of subjects presented at TNM stage iv. These statistics are very different to those in the Western World, so results may not be commensurate with local settings. However, the study does highlight the problem of patients not detecting symptoms early enough and that GOC survival is impaired at the patient interval. With a similar demographic profile, Alimoggadam et al's (2014) retrospective analysis of 368 medical notes revealed that patients with oesophageal and gastric cancer presented with very late staged GOC.

Studies with focus on the patient interval

Five studies presented data relating to advanced stage presentation which could be linked to the patient interval. Subasinghe et al (2010) undertook a 24 month study of patients presenting to a regional centre in Sri Lanka to review where delays may occur in the patient journey. They identified three periods. These were the time from patient first detecting symptoms, to first contact with the health service; first contact to endoscopy; endoscopy to histological confirmation. The study identified the patient interval (first symptom recognition to contact with health department), accounted for 82.2% of the delays, compared with doctor and system

level intervals. However, as with the Malaysian study by Abdullah et al (2010), the ability to generalise findings to a Western context is potentially hampered by the differences in health provision in these countries. Subasinghe et al (2010) acknowledge the lack of available resources for histology and endoscopy and the limited health systems in Sri Lanka. There is no elaboration on how data were collected to determine the first symptom detection and the authors present no information on timing of patient interviews and triangulation of self-reported data. There is no reference made to any tools which were applied to elicit information from patients and the authors have not elaborated on methodological approaches for data analysis. Their descriptive analysis of the cohort is different to the norm, as gender ratio was 1:1 in this study.

A single centre retrospective evaluation of patient notes in America by Schlansky et al (2006) presented data on tumour stage and presentation symptoms in patients with gastroesophageal cancer. Only subjects who had undergone oesophagogastroduodenoscopies who had not been previously diagnosed or treated for GOC were reviewed to reveal disease characteristics and patterns of diagnosis. They found the majority of presentations were staged at T3 or above, revealing a large patient interval delay. The study is somewhat limited through reliance on patient notes to elicit data on clinical symptoms at presentation.

Another American single centre study by Gibbs et al (2007) provided evidence from a retrospective analysis of 307 GOC patients who presented between the years 1991 to 1996. They acknowledge their data is based on subjective patient response on when symptoms were initially detected, but conclude that survival worsens when the time between patient detection and seeking treatment is increased. The study is limited in that authors provide no rationale for choosing the date range of 1991 – 1996. It must be noted that data were old when the research was published in 2007. There is also no elaboration made on sample coverage and completeness of information available in the cancer registry data which was used for extraction.

Smithers et al (2010) presented a secondary analysis of data collected for the larger Australian Cancer Study. This study began with a sample of 3273, but many of these subjects were either non contactable, or had died before the study took place. The strength of this study lies in the pre validated questionnaires used to elicit information on patient symptoms and presentation. However, the total sample was skewed towards survivors and earlier stage presenters. Of 1100 subjects, only 831 had a recorded presentation and symptom history. The authors identify staging information was only available for 7% of patient records, but it is unclear whether this is 7% of the full cohort of 1100, or the 831 with recorded full data. The authors apply a range of cross data analyses to generate TNM staging, generating a figure of 50% of the cohort with staged data. With this, they draw the conclusion that most patients with GOC will present with late stage disease. All of the American studies (Hashemi et al 2009, Schlansky, 2006 and Gibbs, 2007) are extremely useful, but their generalisability is hampered by their single centre status and therefore localised sampling.

The study by Wang et al (2008), offered a comparative analysis of TNM stage I and II diagnosed patients, with TNM stage III and IV to compare delay intervals and their impact on survival. Using similar timeframes as Subasinghe et al (2010) they conclude that symptomatic patients generally wait on average 2-3 months before seeking assistance and that those who present earlier, present with smaller and more localised tumours. They acknowledge the limitations of patient recall and, rarely, are they able to offer a dataset with complete TNM records.

Studies presenting information on the treatment interval

Treatment interval relates to the interval between diagnosis and treatment and involves service level delays. Kotz et al (2006) presented a study to identify whether delays between diagnosis and surgery may have an impact on survival outcome. Data on 800 patients presenting to a

single centre between the years 1995 and 2000 were analysed to assess whether delays between diagnosis and surgery effected survival outcomes. This study found the time taken between histological diagnosis, clinical decision-making and rationalising interventions through multidisciplinary team discussions, improves survival outcomes. Kötz *et al*., (2006) reiterate the importance of undertaking multidisciplinary deliberation on treatment strategies and found that clinically considered interventions receive more favourable outcomes. This is supported in other studies which addressed the total delay interval (Grotenhuis *et al*., 2010).

Discussion

This literature review identifies the patient interval as the most crucial factor for engaging in preventive measures to encourage earlier diagnosis. Most patients present at too late a stage for curation of gastroesophageal cancer. This supports the stance by the UK government and the cancer research (UK) strategy NAEDI (national awareness for early detection and intervention). Encouraging earlier diagnosis is essential to improving cancer survival (Hiom 2015, Neal et al, 2015). A survey of GPs in Scotland published in 2009 (Baughan et al, 2009) identified a disparity in referrals which was dependent on tumour type. General Practitioners (GPs) referred potential breast and skin cancers far more rapidly than other cancers, including those of the upper gastroesophageal, prostate and lung. Kotz et al (2006) identified that GPs were more likely to refer males than females for investigations of suspected GOC, suggesting females had a higher propensity to system delay. Whereas Macleod et al (2009) and McDonald et al (2006) identified males and females exhibited similar wait times to visit a GP with suspected symptoms.

Mcleoud et al (2009) investigated the factors which caused delays in presentation and referrals. Generally, these related to clinical factors such as the severity of symptoms, appropriate awareness and interpretation of symptoms, emotional status of the patient and any support networks they had. Delays in doctor and system levels were attributed to demographic

attributes of patients, how they presented and provided histories and how practitioners responded to cues. McDonald et al (2006) undertook a systematic review of evidence dated from 1970 to 2003, to reveal which factors may be associated with delays in diagnosis of upper gastrointestinal cancers. The authors identified the main patient related factors associated with advanced presenting GOC included low socioeconomic status, non-white ethnicity, presence of pain or bleeding and any symptoms which had effected general functional status. The main system related factors to delays in diagnosis related to initial misdiagnosis of common symptoms and the authors surmised that older males from lower socioeconomic groups were less likely to receive faster referrals. These factors were also evident in the findings of this literature review, which also revealed common attributes of GOC sufferers.

There are several behaviourally modifiable risk factors which may be associated with GOC presentation. The cancer has been previously linked with smoking, obesity and alcohol misuse (Abdullah *et al*., 2010, Macdonald et al, 2006, Parkin, 2011). Some studies link a lower socioeconomic status with the diagnosis (Macleod et al., 2009; Abdullah et al., 2010). Though this is contested in Coupland et al's (2012) study. These authors undertook further evaluation on the cancer site and revealed lower socioeconomic status was more prevalent only in those with upper and mid oesophageal tumours. Many studies report socioeconomic deprivation as an attribute to GOC diagnosis, but these studies are based on limited analysis of site of diagnosis (Abdullah et al, 2010, Bus, 2014, Baughan et al, 2009, Mao, 2011). Akram et al, (2014) identified living in a rural area has been linked to GOC incidence, but this may reflect limited access to services. Many studies link rurality with environmental factors and studies into these are ongoing (Mao, 2011, Zhang, 2013, Mohebbi et al, 2011, Aragones et al , 2007).

All studies in this review linked advanced presentation and delays with worse outcomes. The Royal College of Surgeons' (RCOS) National Oesophagogstric cancer audit (2014) revealed

that when patients were diagnosed through an emergency hospital admissions, they had extremely poor survival outcomes.

The problem with the patient detecting a potential cancer, is that GOC has a very insidious onset and clinical signs may not be clinically detectable until the tumour has reached extensive infiltration (Di Pietro, 2013, Jayasekera, 2012, Lambert, 2012, Yang, 2012). The usual clinical signs are dyspepsia, dysphagia, nausea and vomiting, weight loss, or gastrointestinal bleeding (Wolf et al., 2012). Many papers identify the presence of 'alarm' signals caused patients to seek health advice more rapidly (Hashemi *et al*., 2009; Gibbs *et al*., 2007; Akram *et al*., 2014). Symptoms of weight loss and pain were linked with reduced survival outcomes, but these symptoms were key to patients seeking help (Macdonald *et al*., 2006; Schlansky *et al*., 2006; Macleod *et al*., 2009; Wang *et al*., 2008). However, cachexia – the dramatic loss of weight with cancers – tends to signify the tumour is at advanced stage (Dhanapal et al, 2011).

Much of the evidence on presentation of GOC relies on retrospective cohort studies. Of the 12 papers, 4 were retrospective analysis of existing datasets and these are reliant on country specific definitions of timescales. This literature review evaluated geographically diverse studies and these need to be considered in context. In China, for example, patients are allowed to present directly to the specialist hospital, whereas in the UK, GPs are used as gatekeepers and this may cause system delays.

Public funding and access to healthcare services also has an impact on patient presentation. The UK offers a free national health system to the total population, whereas the United States, for example, uses health insurance and a private health system to enable basic or advanced level access to health-related services. Statistics from each country depend on how patients navigate their journey towards diagnosis. Data will subsequently be skewed by patient's socioeconomic status, access to services and by healthcare funding systems.

Different health systems may not be accurate to capture and record all patient data which is relevant to the underlying condition. This was evident in (Baughan *et al*., 2009) study, where disparities in data collection across health boards resulted in delayed analysis of the first year of results. The UK had similar issues. They retrieved data from 99% of individual trusts across England and Scotland, but Wales did not have sufficient data to complete the national 2013 GOC audit (AUGS, 2013). Even with hospital episode statistics, the audit could still only claim an overall case ascertainment rate for newly diagnosed cancers, to an 85% accuracy (AUGS, 2013).

This review revealed that the majority of studies identified patient interval as most crucial to earlier diagnosis. However, the evidence presented is based on disparate measurements of timescales. For example, Kotz et al (2006) identifies the date of endoscopic biopsy as the date of diagnosis and date of death as the end-point, whereas Gibbs used the date of histlogical confirmation. Others did not identify how this was defined (Coupland et al, 2012, Alimoghaddam, 2014). There was also a range of different diagnostic criteria on which to evaluate survival. Even this was inconsistent – as many studies identified a significant lack of staging data, or presented results for portions of the cohorts under evaluation. This lack of data consistency directly affects underlying quality of the evidence (Weller et al, 2012, Liberati et al, 2009).

There was also a lack of clarity on how and when staging took place. Both Alimoghaddam et al (2014) and Subasinghe and Samarasekera's (2010) studies identified missing TNM staging data Abdullah et al, (2010) reported a 100% data yield, but did not identify how or when staging was undertaken. This was also the case in studies by (Schlansky et al (2006) and Grotenhuis et al (2010). The UK Oesophagogastric Audit reported data were missing in 2819 patients (Royal College of Surgeons, 2014). These variations in the processes of measurement severely threaten internal validity and prevents meta analysis.

Reliance on the degree of tumour proliferation as a measure of how long the cancer has been *in situ* depends on how metabolically active the tumour is. Subasinghe & Samarasekera's study (2010) identify that some tumours may have been present for up to ten years before the patient presents and with little or no suggestive symptoms. Yet Dutta et al (2012) describe a 'doubling time' where extremely metabolically active gastroesophageal tumours can grow and spread extensively. In these cases, early diagnosis and rapid removal is essential to a more favourable outcome. These factors will affect the findings of this literature review, which relied heavily on evidence generated from survival studies.

Throughout the patient journey there are many factors affecting presentation. The patient must suspect there is a problem, the GP must pick up on diagnostic cues, referring appropriately and healthcare systems must run effectively to instigate rapid diagnosis and treatment.

The most crucial period – the 'patient interval' is measured from the date the patient first noticed a symptom, to the date they presented to their GP (Weller 2012). However, there is a significant disparity relating to 'date of first symptom'. It cannot merely be assumed that patients will detect a set of symptoms and will then present to health services to be diagnosed with GOC. There are specific symptoms of GOC presentation, (alarm signals) which are present in almost 50% of cases (Thrift *et al*., 2013; Wallace *et al*., 2001; Fransen *et al*., 2004). However, by the time the patient has symptomatic presentation, the tumour may be far too advanced for curative surgery (Fransen *et al*., 2004; Jones *et al*., 2007)

Patients may present with just one sign of GOC (for example, with 'pain') and subsequently receive analgesia or health related advice. They may then re-present at a different time, with the alarm signals resulting in referral and subsequent diagnosis. The time taken for either the patient or the referral centre to 'notice' GOC related symptoms and seek further assistance, is subject to recall bias from all parties involved. Patients may be poor historians, they may not

identify the full extent of the complaint. Any study investigating delays in the journey attributed to when a patient or a referrer 'noticed' original symptoms needs to be thoroughly scrutinised. The operational definitions underpinning this type of research require objective consideration. This review used evidence from several retrospective case note analyses and findings are dependent on how 'well' the original assessment was documented. Any reports on when patients 'noticed' signs can only be seen as subjective, unless symptoms occurred within days, minutes or hours before presentation. The evidence recording 'time from noticing a symptom, to time to diagnosis or cure' has a significant potential bias.

This literature review also revealed the issue that gastroesophageal cancers tend to be overlooked in the mainstay of literature. Baughan's (2009) study identified 600 cases of oesophageal cancer, but only reported outcomes for the more common breast, colorectal lung and prostate cancers, rather than gastroesophageal cancer and this is common in many cancer research articles. The significant disparity in focussing on the less common cancers is evident. Gastroesophageal cancer patients die early, therefore, follow up is difficult. As a result, this cancer is subject to survivor bias, because patient data are skewed by early subject demise.

Many papers on cancer survival report a 1, 3 or 5 year outcome. However, most GOC diagnoses result in death before two years (Kotz 2006). This affects the data and findings significantly and misses the large number of GOC subjects who die within the first 6 or 8 months. A reclassification of diagnostic criteria would allow for this skew in GOC survival.

Limitations

Gastroesophageal cancer is prevalent across the globe, but more prevalent in middle and far Eastern countries, where English is not the primary language. This means there may be evidence published in other languages which was not identified in this review. As identified in the discussion, the range of different timescales and nomenclature applied in cancer research

have an impact on results. To identify when a patient actually detected their first symptoms is hampered by several confounding factors. The patient journey through many different healthcare systems is also complex. How patients present in China may differ significantly, to how they present in the US, or UK for example.

Other factors which have an impact on presentation and survival in gastroesophageal cancer are the underlying aetiology, the cancer site, the patient attributes and comorbidities. Most of these patients are elderly, so the presence of several other conditions and illnesses is fairly common in this cancer.

Conclusion

This review of GOC specific evidence identified that the patient interval is the most crucial period to encourage earlier presentation. It also highlighted disparate processes of measurement and sampling in cancer research articles. The incidence of gastroesophageal cancer is increasing across the globe, yet survival remains poor. However, there is a significant lack of focus on this cancer in the literature. Further research is essential to evaluate factors which potentially cause unnecessary delays in the diagnostic journey. Potential sufferers of this cancer need to be encouraged to seek medical attention as the patient interval is the most crucial to survival. For this, community level interventions are required to raise awareness of the signs and symptoms of this cancer.

References

Abdullah, M., Karim, A.A. & Goh, K. (2010) Late presentation of esophageal cancer: observations in a multiracial South-East Asian population. *Journal of Digestive Diseases,* 11 (1), 28-33.

ABDULLAH, M., KARIM, A.A. & Khean-Lee, G.O.H. (2010) Late presentation of esophageal cancer: Observations in a multiracial South–East Asian population. *Journal of Digestive Diseases,* 11 (1), 28-33.

Adair, T., Hoy, D., Dettrick, Z. & Lopez, A., D. (2011) Trends in oral, pharyngeal and oesophageal cancer mortality in Australia: the comparative importance of tobacco, alcohol and other risk factors. *Australian & New Zealand Journal of Public Health,* 35 (3), 212-219.

Akram, M., Siddiqui, S.A. & Karimi, A.M. (2014) Patient Related Factors Associated with Delayed Reporting in Oral Cavity and Oropharyngeal Cancer. *International Journal of Preventive Medicine,* 5 (7), 915-919.

Alimoghaddam, K., Jalali, A., Aliabadi, L.S., Ghaffari, F., Maheri, R., Eini, E., Mashhadireza, M., Mousavi, S.A., Bahar, B., Jahani, M. & Ghavamzadeh, A. (2014) The outcomes of esophageal and gastric cancer treatments in a retrospective study, single center experience. *International Journal of Hematology-Oncology and Stem Cell Research,* 8 (2), 9-13.

Allum, W.H., Griffith, S.M., Watson, A. & Colin-jones, D. (2002) Guidelines for the management of oesophageal and gastric cancer. *GUT,* 50 (5), v1-v23.

Aragones, N., Ramis, R., Pollan, M., Perez-Gomez, B., Gomez-Barrosso, D., Lope, V., Boldo, E.i., Garcia-Perez, J., Lopez-Abente, G. (2007) Oesophageal cancer mortality in Spain - A spatial analysis Bioned Central Cancer 7 (3) available at http;//www.biomedcentral.com/1471-2407/7/3

Baughan, P., O'Neill, B. & Fletcher, E. (2009) Auditing the diagnosis of cancer in primary care: the experience in Scotland. *British Journal of Cancer,* 101 S87-S91.

Braun, V., & Clarke, V. (2006). Using thematic analysis in psychology. *Qualitative Research*

in Psychology, 3(2), 77-101.

Coupland, V.H., Allum, W., Blazeby, J.M., Mendall, M.A., Hardwick, R.H., Linklater, K.M., Moller, H. & Davies, E.A. (2012) Incidence and survival of oesophageal and gastric cancer in England between 1998 and 2007, a population-based study. *BMC Cancer,* 12 11.

Chadwick, G., Groene, O., Cromwell, D., Hardwick, R.H., Riley, S., Crosby, T.D.L. and Greenaway, K., (2013),
The National Oesophago-Gastric Cancer Audit London, Health and Social Care Information Centre.

Crowe, M., & Sheppard, L. (2011). A review of critical appraisal tools. Journal of Clinical Epidemiology, 64(1), 79-89

Dixon-Woods, M., Bonas, S., Booth, A., Jones, D., Miller, T., & Sutton, A. (2006) How can systematic reviews incorporate qualitative research? A critical perspective. *Qualitative Research,* 6, 27-44.

Dutta, S., Going, J.J., Crumley, A.B., Mohammed, Z., Orange, C., Edwards, J., Fullarton, G.M., Horgan, P.G. & McMillan, D.C. (2012) The relationship between tumour necrosis, tumour proliferation, local and systemic inflammation, microvessel density and survival in patients undergoing potentially curative resection of oesophageal adenocarcinoma. *British Journal of Cancer,* 106 (4), 702-710.

Fransen, G.A.J., Janssen, M.J.R., Muris, J.W., Laheij, R.J.F. & Jansen J.B.M.J. (2004) Meta analysis : The diagnostic value of alarm symptoms for upper gastrointestinal malignancy. *Alimentary Pharmacology & Therapeutics,* 20 1045-1052.

Gibbs, J.F., Rajput, A., Chadha, K.S., Douglas, W.G., Hill, H., Nwogu, C., Nava, H.R. & Sabel, M.S. (2007) The changing profile of esophageal cancer presentation and its implication for diagnosis. *Journal of the National Medical Association,* 99 (6), 620-626.

Grotenhuis, B.A., Van Hagen, P., Wijnhoven, B.P.L., Spaander, M.C.W., Tilanus, H.W. & Van Lanschot, Jan J. B. (2010) Delay in Diagnostic Workup and Treatment of Esophageal Cancer. *Journal of Gastrointestinal Surgery,* 14 (3), 476-483.

Hashemi, N., Loren, D., DiMarino, A.J. & Cohen, S. (2009) Presentation and prognosis of esophageal adenocarcinoma in patients below age 50. *Digestive Diseases and Sciences,* 54 (8), 1708-1712.

Hawker, S., Payne, S., Kerr, C., Hardey, M. & Powell, J. (2002) Appraising the evidence: reviewing disparate data systematically. *Qualitative Health Research,* 12 (9), 1284-1299.

JBI. (2014). *Joanna Briggs Institute Reviewers' Manual 2014. Methodology for JBI Mixed Methods Systematic Reviews.* Adelaide: JBI.

Jones, R., Latinovic, R., Charlton, J. & Gulliford, M.C. (2007) Alarm symptoms in early diagnosis of cancer in primary care: cohort study using General Practice Research Database. *BMJ: British Medical Journal (International Edition),* 334 (7602), 1040-1044.

Kötz, B.S., Croft, S. & Ferry, D.R. (2006) Do delays between diagnosis and surgery in resectable oesophageal cancer affect survival? a study based on West Midlands cancer registration data. *British Journal of Cancer,* 95 (7), 835-840.

Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gotzsche, P.C., Ioannidis, J.P., Clarke, M., Devereaux, P.J., Kleijnen, J. & Moher, D. (2009) The PRISMA statement for reporting

systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of Clinical Epidemiology,* 62 (10), e1-34.

Macdonald, S., Macleod, U., Campbell, N.C., Weller, D. & Mitchell, E. (2006) Systematic review of factors influencing patient and practitioner delay in diagnosis of upper gastrointestinal cancer. *British Journal of Cancer,* 94 (9), 1272-1280.

Macleod, U., Mitchell, E.D., Burgess, C., Macdonald, S. & Ramirez, A.J. (2009) Risk factors for delayed presentation and referral of symptomatic cancer: evidence for common cancers. *British Journal of Cancer,* 101 Suppl 2 S92-S101.

Mao, W.M., Zheng, W.H., Ling, Z.Q. (2010) Epidemiologic risk factors for gastroesophageal cancer development *Asian Pacific Journal for Cancer Prevention* 12 (10) 146 1-6

Medical research Council (2002) Surgery with or without preoperative chemotherapy in oesophageal cancer; a randomised controlled trial. *Lancet,* 359 1727-1733.

Moher, D., Liberati, A., Tetzlaff, J. & Altman, D. (2009) Preferred reporting items for systematic reviews and meta analyses : the PRISMA statement. *PLoS Med,* 6 (6), .

Moher, D., Altman, D.G., Liberati, A. & Tetzlaff, J. (2011) PRISMA statement. *Epidemiology (Cambridge, Mass.),* 22 (1), 128; author reply 128.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G. & PRISMA Group (2010) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *International Journal of Surgery (London, England),* 8 (5), 336-341.

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A. & PRISMA-P Group (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews,* 4 (1), 1-4053-4-1.

Mohiebbi, M., Wolfe, R., Jolley, D., Forbes, A., Mahmoodi, M., Burton, R.C. (2011) The spatial distribution of oesophageaL AND GASTRIC CANCER IN THE Caspian Region of Iran, An ecological analysis of diet and socioeconomic influences. *International journal of health Geographics* 10 (13)

National Institute for Health and Clinical Excellence, (2005), *Referral Guidelines for suspected cancer.* Clinical Guideline 27, UK, NIHCE.

Neal, R.D., Tharmanathan, P., France, B., Din, N.U., Cotton, S., Fallon-Ferguson, J., Hamilton, W., Hendry, A., Hendry, M., Lewis, R., Macleod, U., Mitchell, E.D., Pickett, M., Rai, T., Shaw, K., Stuart, N., Torring, M.L., Wilkinson, C., Williams, B., Williams, N. & Emery, J. (2015) Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. *British Journal of Cancer,* .

NHS The Information Centre, (2008), *National Oesophagogastric Cancer Audit.* First Annual report, The NHS Information centre.

Nuting, C.M., Robinson, M. & Birchall, M. (2008) Survival from Laryngeal cancer in England and Wales up to 2001. *British Journal of Cancer,* 99 (1), s38-s39.

Office for National Statistics, (2005), *Cancer Statistics Registrations: Registrations of cancer diagnosed in 2005.* 36, ONS.

Orengo, M.A., Casella, C., Fontana, V., Filiberti, R., Conio, M., Rosso, S., Tumino, R., Crosignani, P., De Lisi, V., Falcini, F. & Vercelli, M. (2006) Trends in incidence rates of oesophagus and gastric cancer in Italy by subsite and histology, 1986-1997. *European Journal of Gastroenterology & Hepatology,* 18 (7), 739-746.

Parkin, D.M., Boyd, L., Walker, L.C. (2011) The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. *British Journal of Cancer.* 105(S2) S77-S81.

Read more at http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer/risk-factors#gcFrZACc3SJSFYmW.99

Pluye, P., Gagnon, M., Griffiths, F.., Johnson-Lafleur, J. (2009) A scoring system for appraising mixed methods research and concomitantly appraising qualitative, quantitative and mixed methods primary studies in mixed studies reviews International Journal of Nursing Studies 46. 529–546

Pluye, P., Robert, E., Cargo, M., Bartlett, G., O'Cathain, A., Griffiths, F., Boardman, F., Gagnon, M.P., & Rousseau, M.C. (2011). *Proposal: A mixed methods appraisal tool for systematic mixed studies reviews.* Department of Family Medicine, McGill University, Montreal, Canada. Available at from http://mixedmethodsappraisaltoolpublic.pbworks.com. Archived by WebCite® at http://www.webcitation.org/5tTRTc9yJ accessed 031016

Pluye, P. & Hong, Q.N. (2014). Combining the power of stories and the power of numbers: Mixed Methods Research and Mixed Studies Reviews. *Annual Review of Public Health,* 35, 29-45.

Richards, M.A. (2009a) The size of the prize for earlier diagnosis of cancer in England. *British Journal of Cancer,* 101 Suppl 2 S125-9.

Richards, M.A. (2009b) The size of the prize for earlier diagnosis of cancer in England. *British Journal of Cancer,* 101 Suppl 2 S125-9.

Royal College of Surgeons, (2014), *National Oesophagogstric Cancer Audit progress report 2014.* UK, Royal College of Surgeons of England.

Schlansky, B., Dimarino, A.J., J., Loren, D., Infantolino, A., Kowalski, T. & Cohen, S. (2006) A survey of oesophageal cancer: pathology, stage and clinical presentation. *Alimentary Pharmacology & Therapeutics,* 23 (5), 587-593.

Shamseer, L., Moher, D., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A. & PRISMA-P Group (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ (Clinical Research Ed.),* 349 g7647.

Sloggett, A., Young, H. & Grundy, E. (2007) The association of cancer survival with four socioeconomic indicators : a longitudinal study of the older population of England and Wales 1981 - 2000. *BMC Cancer,* 7 (20), .

Smithers, B.M., Fahey, P.P., Corish, T., Gotley, D.C., Falk, G.L., Smith, G.S., Kiroff, G.K., Clouston, A.D., Watson, D.I. & Whiteman, D.C. (2010) Symptoms, investigations and management of patients with cancer of the oesophagus and gastro-oesophageal junction in Australia. *The Medical Journal of Australia,* 193 (10), 572-577.

Subasinghe, D. & Samarasekera, D.N. (2010) Delay in the diagnosis of esophageal carcinoma: experience of a single unit from a developing country. *Indian Journal of Cancer,* 47 (2), 151-155.

Thrift, A.P., Kendall, B.J., Pandeya, N. & Whiteman, D.C. (2013) A Model to Determine Absolute Risk for Esophageal Adenocarcinoma. *Clinical Gastroenterology and Hepatology,* 11 (2), 138-144.e2.

Wallace, M.B., Durkalski, V.L. & Vaughan, J. (2001) Age and alarm signals do not predict endoscopic findings among patients with dyspepsia : A multicentre database study. *Gut,* 49 29-34.

Wang, J., Liu, F., Gao, H., Wei, W., Zhang, X., Liang, Y. & Cheng, Y. (2008) The symptom-to-treatment delay and stage at the time of treatment in cancer of esophagus. *Japanese Journal of Clinical Oncology,* 38 (2), 87-91.

Weller, D., Vedsted, P., Rubin, G., Walter, F.M., Emery, J., Scott, S., Campbell, C. andersen, R.S., Hamilton, W., Olesen, F., Rose, P., Nafees, S., van Rijswijk, E., Hiom, S., Muth, C., Beyer, M. & Neal, R.D. (2012) The Aarhus statement: improving design and reporting of studies on early cancer diagnosis. *British Journal of Cancer,* 106 (7), 1262-1267.

Zheng, S., Vuitton, L., Sheyhidin, I., Vuitton, D.A., Zhang, Y. & Lu, X. (2010) Northwestern China: a place to learn more on oesophageal cancer. Part one: behavioural and environmental risk factors. *European Journal of Gastroenterology & Hepatology,* 22 (8), 917-925.

Zhang, Y. (2013) Epidemiology of esophageal cancer *World Journal of gastroenterology* 19 (34) 5598-606