Barrett's oesophagus and oesophageal cancer following oesophageal atresia repair - a systematic review

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Funding: The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. Lucinda Tullie is funded by the NIHR Great Ormond Street Hospital Biomedical Research Centre and George Bethell is funded by the NIHR Academic Clinical Fellow program.

The authors wish to acknowledge the RCSEng Clinical Research Initiative who provided educational support for this review.

Submission as a **Review article**

Abstract

Background

Concern exists that patients born with oesophageal atresia (OA) may be at high risk for Barrett's oesophagus (BO), a known malignant precursor to the development of oesophageal adenocarcinoma. Screening endoscopy has a role in early BO identification but is not universal in this population. This study aimed to determine prevalence of BO, following OA repair surgery, to quantify the magnitude of this association and inform the need for screening **and surveillance**.

Method

A systematic review, undertaken according to PRISMA guidelines, was pre-registered on PROSPERO (CRD42017081001). PubMed and EMBASE were interrogated using a standardized search strategy on 31/7/20. Included papers, published in English, reported either: one or more **cases of** either BO (gastric/intestinal metaplasia) or oesophageal cancer in patients born with OA; or long term (>2 years) follow-up after OA surgery with or without **endoscopic screening or surveillance.**

Results

134 studies were identified including 19 case reports/ series and 115 single or multi-centre cohort studies. There were 13 cases of oesophageal cancer (9 squamous cell, 4 adenocarcinoma) with a mean age at diagnosis was 40.5 years (range 20-47). From 6282 patients under long-term follow-up, 317 patients with BO were reported. Overall prevalence of BO was 5.0% (95%CI 4.5-5.6%)with a mean age at detection of 13.8 years (range 8 months–56 years). Prevalence of BO in series reporting long-term endoscopic follow-up was 12.8% (95%CI 11.3-14.5%).

Conclusion

Despite a limited number of cancers, the prevalence of BO in patients born with OA is relatively high. While limited by the quality of available evidence, this review suggests endoscopic screening and surveillance may be warranted but uncertainties remain over the design and effectiveness of any putative programme.

Introduction

A number of reports have described oesophageal adenocarcinoma and squamous cell carcinoma arising in adult survivors of oesophageal atresia (OA).[1-6] The development of gastric and intestinal metaplasia in the oesophagus during childhood, adolescence or early adulthood has been widely documented.[7-16] These observations lead to the question of how these patients should be followed up to permit prompt detection of premalignant oesophageal mucosal changes. Currently, there is little consensus on either requirement for, or timing of, endoscopic screening or surveillance in patients born with OA.

Gastro-oesophageal reflux (GOR) is common following OA repair. The aetiology is likely contributed to by impaired oesophageal motility as well as disruption of the inherent anti-reflux mechanisms as a consequence of mobilisation required to achieve an oesophageal anastomosis. The oesophageal mucosa may then be subjected to repeated exposure to refluxate that precipitates metaplasia. An international consensus statement has defined paediatric Barrett's oesophagus (BO) as oesophageal metaplasia that is intestinal metaplasia positive or negative.[17]

Replacement of normal squamous epithelium in the distal oesophagus with columnar epithelium as consequence of GOR, encompasses at least three different epithelial patterns. These are an intestinal-type usually harbouring mucous and goblet cells, as well as gastric fundus- or cardiac-types. Current evidence suggests that intestinal metaplasia represents the highest risk for subsequent dysplasia culminating in adenocarcinoma.[18] Controversy exists regarding the degree of malignant potential attributable to gastric metaplasia.[19]

BO is frequently occult, poorly correlated with the presence of reflux symptoms. One study reported no association between presence of symptoms of GOR in patients aged 15-19 with and without histological evidence of BO.[7] Symptoms alone cannot be used to identify BO.

Whilst BO is well recognised following OA repair, the scale of the problem and associated morbidity has not been quantified beyond a handful of studies.[13,20-22] Without this evidence it is difficult to determine whether endoscopic screening and surveillance is indicated.

The primary aim of this review was to determine the prevalence of BO and oesophageal cancer in children, adolescents and adults born with OA to determine whether endoscopic screening and surveillance might be indicated. The secondary aim was to assimilate data to inform the design of any such surveillance programme in this population.

Methods

This review was performed in accordance with the PRISMA guidelines for systematic reviews and according to a defined protocol registered with PROSPERO (York University, York, United Kingdom) prior to commencing the review (CRD42017081001).[23,24]

Search strategy

The search strategy was deliberately broad in order to be comprehensive and included studies reporting cases of BO and/or oesophageal cancer in patients with repaired OA, in addition to those documenting long-term follow-up of patients born with OA. Several types of article were included in order to ensure that the search was systematic and that the findings would be as robust as possible. In addition to focusing on articles reporting outcomes of patients with OA, articles reporting cohorts of children having anti-reflux procedures or upper gastrointestinal endoscopy (UGIE) were also examined since these may have included patients born with OA. Searches were performed on 31st July 2020 using both the PubMed and Embase databases. In all databases, adjacency operators and truncation symbols were used in text word searches when appropriate to capture variations in phrasing and expression of terms. All synonymous terms were combined first using the Boolean "OR." The three distinct concepts related to intervention, population, and study design were combined with the Boolean "AND". No language or date restrictions were applied. The detailed search strategy for each database used is included in in Supporting information Figure S1. As well

as using these databases, references in systematic reviews and randomized controlled trials, found in the search, were also included.

Study inclusion criteria

Articles that met one or both of the following criteria were included: any study that reported at least one patient with BO or oesophageal cancer who had undergone either oesophageal atresia repair or oesophageal replacement having been born with OA; or any study that reported long term follow-up (defined as minimum 2 years) of patients following oesophageal atresia repair or replacement regardless of whether they included BO or oesophageal cancer, and regardless of the use of endoscopic screening (a single endoscopy) or surveillance (a programme of sequential endoscopies).

All study types were eligible for inclusion, including cohort studies and systematic reviews, with or without meta-analysis, and case reports. For the purposes of the search, a wide definition of BO was used that included any definition used by source article authors, including both gastric and intestinal metaplasia and heterotopic gastric mucosa.

Study exclusion criteria

Studies were excluded if the patients only had a H-type tracheoesophageal fistula (TOF) without OA. Studies were also excluded if they were abstracts only from conference presentations or published in non-English language. Where multiple reports from the same centre or authors were identified that resulted in duplication of cases or patient cohorts, either the first reporting study, or the largest, in terms of patient numbers was included.

Article selection

Two reviewers independently assessed each title and abstract of all identified citations. Full-text articles were obtained if either reviewer considered the citation potentially relevant with a low threshold for retrieval. Full texts of selected studies were then critically reviewed to assess eligibility. Reasons for exclusion of studies were recorded. The final set of studies included in the systematic review was determined by consensus. The online resource Rayyan was used to assist with article

screening and selection.[25] *A priori* it was decided not to use any risk of bias assessment tool and as it was anticipated that all studies would likely be observational in nature, no study would be excluded based on methodology alone.

Data extraction

Data were extracted independently, reviewed to ensure accuracy and entered into an electronic database recording paper title and author, study type, number of patients, length of follow-up, detail of endoscopic screening and/or surveillance, number of patients with BO/oesophageal cancer.

Outcomes

The following outcomes were selected *a priori*: the number of patients with oesophageal cancer born with OA: the overall prevalence of BO and oesophageal cancer in patients born with OA: and the prevalence of BO and oesophageal cancer in patients born with OA who had undergone endoscopic screening or surveillance.

Further relevant clinical details of any patient with oesophageal cancer born with OA (such as age at diagnosis, type and site of cancer, detection method and outcome) were recorded as available, as were details of endoscopic screening or surveillance programmes and clinical details of patients with BO identified at endoscopy. For the purposes of reporting in this review, intestinal metaplasia was defined as metaplastic change alongside the presence of goblet cells and gastric metaplasia defined as metaplastic change without goblet cells.

Statistical analysis

Data were entered and stored in an Excel (Microsoft, USA) spreadsheet, descriptive analysis of data was undertaken using SPSS V.25 (IBM, Armonk, New York, United States of America). Data are reported as mean, median and range. The overall prevalence of BO and oesophageal cancer in patients born with OA was calculated by dividing the number of individuals with either BO or oesophageal cancer reported among the total population of oesophageal atresia patients by the total number of patients. The prevalence amongst the population who had undergone endoscopic screening or surveillance was calculated in a similar way, but limiting denominator population to those who had undergone one or more endoscopies.

Results

Characteristics of included studies

A total of 134 articles met the inclusion criteria. Details of excluded articles are shown in Figure 1 including unavailability (3), conference abstract only (59), review article (16) and those which did not meet the inclusion criteria (58) involving short or unclear follow-up duration, wrong or mixed study population or disease process. (such as oesophageal replacement in which OA and non-OA populations could not be separated) There were no cases of BO nor oesophageal carcinoma in these excluded studies. Populations published in multiple reports from the same centre were also excluded (11).[26-36]

The 134 articles were published between 1972 and 2020 and included 10 case reports and 9 case series, reporting one or more cases of BO or oesophageal cancer in OA patients, and 115 either single or multi-centre cohort studies documenting long-term follow-up of OA patients with or without endoscopic screening or surveillance. These involved a total of 6282 OA patients with long-term follow-up (>2 years) following either primary repair and/or oesophageal replacement. This total population figure was used as the denominator for the subsequent calculation of BO and oesophageal cancer prevalence. Median individual study population size was 87 (42-870) patients. The 6282 OA patients comprised both those who were documented to have undergone endoscopy during follow-up, including 1727 who had endoscopic screening or surveillance.

Oesophageal cancer

There were 13 patients with oesophageal cancer identified in 7 cohort studies and case reports from 4 centres in 3 countries (Table 1). Median age at diagnosis of oesophageal cancer was median 40.5 years (range 20-47) and 4 were adenocarcinomas and 9 squamous cell carcinomas (SCC). Five tumours were detected in the mid/distal oesophagus, three were adjacent to the site of the oesophageal anastomosis and two were in interposed segments replacing oesophagus (skin and colon).[1,2,5,6,37] Three patients, two with adenocarcinoma and one with SCC, also had endoscopic evidence of BO.[1,2,5] There was one patient, with BO and low grade dysplasia, in whom SCC was

detected at surveillance endoscopy.[5]

At last recorded follow-up, 5 patients were alive, having completed treatment, 5 patients were receiving ongoing treatment and 3 had died (Table 1).

The overall prevalence of oesophageal cancer in OA patients under long term follow-up was 0.002% (13/6282) with a prevalence of 0.06% (1/1727) in the cohort who had undergone either endoscopic screening or surveillance.

Barrett's oesophagus

Three-hundred and seventeen patients with BO were reported in 48 cohort studies and case reports from 30 centres in 18 countries,[7-10,12-16,20-22,38-73] representing all reported patients with BO under long-term follow-up for OA.

Of these, intestinal metaplasia was identified in 54, gastric metaplasia in 227, low grade dysplasia in one, heterotopic gastric mucosa in 3 patients and type of metaplasia unspecified in 38.

The overall prevalence of BO in OA patients under long term follow-up was 5.0% (317/6282) (95% CI 4.5-5.6%) (Supporting information Figure S2). The mean age at detection of BO was 13.8 years, median 16 years (range 8 months-56 years).

Endoscopic screening and surveillance

There were 1727 patients who underwent one or more endoscopies +/- biopsies during OA follow-up. The twenty-four studies in which either endoscopic screening or surveillance were undertaken are summarised in Table 2.[7-10,12-15,20-22,49,51,56-60,68,73-77] They report endoscopies performed in defined OA populations with known numbers.

Twenty studies reported results of endoscopic screening; a single endoscopy to assess for BO, which was undertaken at mean age of 20 years (median 16 years, range 16 months-57 years),[7,9,10,12-15,20,46,48,54-58,68,74-76] Whilst many of these studies, reporting screening endoscopies, suggested a requirement for further surveillance, when BO was identified, few studies subsequently outlined their proposed surveillance regimen.[68]

Two studies reported the results of a combination of screening and surveillance endoscopies, but did not report the age range at which these were undertaken.[22,73] Two studies reported endoscopic

surveillance in paediatric populations.[9,21] The first study reported results from 3-yearly surveillance endoscopies from the age of 3 years until transition to adult care.[9] Additional "off schedule" endoscopies were undertaken in children with severe reflux in whom surgical intervention was under consideration.[9] In the second study, surveillance endoscopies were undertaken at 1,3,5,10,15 and >15 years until the age of 17.[21]

There were 221 patients with BO (intestinal metaplasia, 49; gastric metaplasia,170; metaplasia type unspecified, 2). The prevalence of BO in the cohort who had undergone endoscopic screening or surveillance was 12.8% (221/1727) (95% CI 11.3-14.5%) (range per series 0-42.5%).[7-10,12-15,20-22,49,51,56-60,68,73-77] Intestinal metaplasia was detected at a mean age of 38.5 years (median 38.5) and gastric metaplasia at a mean age of 9.5 years (median 16.5), range 2-56 years.
In those detected before the age of 16, identified by paediatric endoscopies respectively, of the 49 patients with intestinal metaplasia, 11 were ≤ 15 years and 38 >15 years. Among those with gastric metaplasia 60 patients were ≤ 15 years and 101 were >15 years.

From studies reporting endoscopic surveillance, in 6 patients gastric metaplasia preceded intestinal metaplasia on sequential endoscopies, with gastric metaplasia occurring 1-5 years prior.[21,22] Whilst there were two reported cases of resolution of BO (1 gastric and 1 intestinal) either spontaneously or following anti-reflux treatment, the majority of BO persisted.[9,47,66] Gastric and intestinal metaplasia were present concurrently at screening endoscopy in 4 patients.[22] Three patients had intestinal metaplasia associated with low grade dysplastic changes at screening endoscopy.[51] A single oesophageal cancer (SCC) was reported in the population who had undergone endoscopic surveillance.[5,51]

Discussion

This systematic review identified a notable global prevalence of BO in this population, highest in those who had undergone endoscopic screening. Oesophageal cancer, following OA repair or replacement remained rare, however, with just 13 patients reported, the majority of whom had SCC not adenocarcinoma. Only a single cancer (an SCC) was picked up by endoscopic surveillance.

The present review should be considered in the context of increasing concern that patients born with oesophageal atresia are at increased risk for developing oesophageal cancer. [5,48,68,78] Although the absolute number of cases of oesophageal cancer identified was relatively low, the likelihood of under-reporting seems considerable. The majority of studies reported follow-up in the paediatric period, in patients ≤ 15 years, whereas all cancer diagnoses have occurred in adulthood with a mean age at diagnosis of 40 years. As there are no population-based cohort studies of patients born with oesophageal atresia being followed into adult life, it is not possible to define with certainty the true prevalence of oesophageal cancer in this population. The closest estimate is a population-based study from Finland of 272 patients born with oesophageal atresia with median 35 years of follow-up. No patients with oesophageal cancer were identified.[11] With a background incidence of oesophageal cancer in Finland at the time of 4.3 per 100,000 they were only able to exclude a prevalence of oesophageal cancer in patients born with oesophageal atresia of greater than 500 times that of the background population. Of note, patients in the present analysis developed oesophageal cancer at a younger age (median 40.5 years) than the general population where the median age at diagnosis is around 64 years.[79]

BO is a recognised precursor to oesophageal adenocarcinoma, implying that endoscopic screening and surveillance of at risk individuals, such as those with OA, might identify pre-malignant change and permit early interventions.[80] Based on the present review an overall prevalence of BO in patients born with OA appears to be about 5% in a mixed screened and unscreened population, rising to around 13% in the screening and surveillance cohort. This is notably higher than the background prevalence of BO in both adult and paediatric populations; reported at 1.3-1.6% and 0.002% respectively,.[81-83]

Despite this high prevalence, no patient under endoscopic surveillance was identified in the present series who progressed to adenocarcinoma. However, the majority of studies included in the review

report cases of BO identified from screening rather than surveillance endoscopies. Although prevalence rates from screening suggest that endoscopic surveillance may be justified, it is unclear to what extent it would be either clinically beneficial or cost-effective.

A range of screening and surveillance programmes were identified in the present review. The youngest patient identified with BO (gastric metaplasia) was aged 8 months.[42] Intestinal metaplasia, has been reported in a patient as young as two.[22] In the present study, 1 in 5 cases of intestinal metaplasia and one third of gastric metaplasia cases, detected by endoscopic screening, were in children ≤ 15 years. This may be taken to suggest that screening should start during childhood and indeed some authors have advocated that screening should commence during the teenage years or early 20s.[7,9,48] The optimal frequency of surveillance in this population also remains unclear. ESPGHAN guidance recommends three surveillance endoscopies during childhood in asymptomatic patients with treated OA; after stopping anti-reflux therapy, before the age of 10 years and a further endoscopy on transition to adult care.[84] Current adult guidelines recommend surveillance endoscopies 2-5 yearly depending upon the length and type of BO, with more frequent surveillance advised when dysplastic changes are present.[19,85]

In line with guidelines, the present review included both gastric and intestinal metaplastic change in the definition of Barrett's oesophagus.[19] This may explain why the prevalence of BO was as high as 43% in one study.[7] Intestinal metaplasia, is generally considered to be the significant risk factor for malignancy, specifically adenocarcinoma,[86] although the relative risks associated with gastric metaplasia; columnar epithelium without goblet cells, remains a subject of controversy.[18,87] In the absence of documented progression of BO to oesophageal cancer in patients born with oesophageal atresia, in the present review the importance of either gastric or intestinal epithelial metaplasia in this population cannot be evaluated.

A notable observation in the present review was the preponderance of SCC rather than adenocarcinoma. In the absence of a recognizable precursor lesion for SCC, this suggests that

endoscopic surveillance based on BO would be ineffective. Until there are a sufficient number of high quality studies with follow-up over a long time period no firm conclusions can be drawn.

Despite the present study being limited by the quality of existing available evidence, the broad approach to identifying patients at risk and wide study inclusion criteria has proved informative. Few studies documented prospective endoscopic screening and surveillance programmes and this limits the ability to make comparisons between different screening or surveillance programmes. In view of the numbers involved, international collaborative studies should be undertaken to identify the optimal screening and surveillance programs in this population and assess their clinical and cost-effectiveness.

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