Original article

Effect of surveillance of Barrett's oesophagus on the clinical outcome of oesophageal cancer

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Background: **Surveillance programmes for Barrett's oesophagus have been implemented in an effort to detect oesophageal adenocarcinoma at an earlier and potentially curable stage. The aim of this study was to examine the impact of endoscopic surveillance on the clinical outcome of patients with adenocarcinoma complicating Barrett's oesophagus.**

Method: **Consecutive patients who underwent oesophageal resection for high-grade dysplasia or adenocarcinoma arising from Barrett's oesophagus were studied retrospectively. The pathological stage and survival of patients identified as part of a surveillance programme were compared with those of patients presenting with symptomatic adenocarcinoma.**

Results: **Seventeen patients in the surveillance group and 74 in the non-surveillance group underwent oesophagectomy. Disease detected in the surveillance programme was at a significantly earlier stage: 13 of 17 *versus* 11 of 74 stage 0 or I, three *versus* 26 stage II, and one *versus* 37 stage III or IV ($P < 0{\cdot}001$). Lymphatic metastases were seen in three of 17 patients in the surveillance group and 42 of 74 who were not under surveillance ($P = 0{\cdot}004$). Three-year survival was 80 and 31 per cent respectively ($P = 0{\cdot}008$).**

Conclusion: **Patients with surveillance-detected adenocarcinoma of the oesophagus are diagnosed at an earlier stage and have a better prognosis than those who present with symptomatic tumours.**

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Introduction

The incidence of oesophageal adenocarcinoma has increased dramatically over the past three decades and now accounts for approximately two-thirds of all oesophageal cancers in the West[1,2]. Adenocarcinoma is usually preceded by Barrett's oesophagus, in which the squamous epithelium of the lower oesophagus is replaced by a metaplastic columnar epithelium. Barrett's oesophagus is found in 3–5 per cent of patients undergoing endoscopy for symptoms of gastro-oesophageal reflux[3]. Although its prevalence is unknown, an autopsy study has indicated that only one in 17 cases of Barrett's oesophagus in the general population are diagnosed clinically[4]. The reported incidence of adenocarcinoma in patients with Barrett's oesophagus ranges from one in 52 to one in 441 patient-years of follow-up[5–10].

Despite recent advances in the diagnosis and management of oesophageal cancer, the prognosis remains dismal, with a 5-year survival rate of 10 per cent[11–13]. However, patients with early (T1) tumours have a more favourable prognosis, and 5-year survival rates exceeding 60 per cent have been reported in surgical series[14–16]. Furthermore, it has been shown that in most patients the development of invasive carcinoma involves a slow multistep progression through worsening degrees of dysplasia[6,17,18]. Periodic endoscopic surveillance of patients with Barrett's oesophagus has therefore been advocated, with the aim of detecting disease at an early and potentially curable stage. Because high-grade dysplasia and intramucosal carcinomas have no distinctive macroscopic features[19], endoscopic surveillance relies on systematic biopsy for the detection of early tumours[20].

The value of surveillance programmes has been questioned in terms of cost[21], the low yield of adenocarcinomas[9,22], and lack of evidence that surveillance improves the overall survival of patients with Barrett's oesophagus[22–24]. It was shown previously in Leeds that the incidence of adenocarcinoma in patients with specialized Barrett's epithelium is one in 95 patient-years of follow-up[10]. The aim of the present study was to examine

the impact of endoscopic surveillance on the pathological stage and clinical outcome of adenocarcinoma arising in Barrett's oesophagus.

Patients and methods

Patients with carcinoma of the oesophagus or gastro-oesophageal junction who underwent resection at Leeds General Infirmary between January 1990 and December 2000 were identified retrospectively from histopathology and operating theatre records. Patients who had undergone surgery for high-grade dysplasia or invasive adenocarcinoma arising from a segment of Barrett's oesophagus were identified from the pathology reports of the resected specimens. Those with locally advanced tumours who had undergone neoadjuvant treatment (chemotherapy, radiotherapy or a combination of the two) were excluded from this analysis because their disease could not be staged accurately. Barrett's oesophagus was defined as a change in the oesophageal mucosa of any length that was visible endoscopically or on inspection of the surgical specimen, and that demonstrated intestinal metaplasia on histological examination. Consequently, patients with 'short-segment' Barrett's oesophagus (length less than 3 cm) were included, whereas those with intestinal metaplasia confined to the gastro-oesophageal junction (not visible) were excluded from the study.

Clinical and pathological data were collected for all patients, who were divided into two groups. The first group comprised patients who developed high-grade dysplasia or adenocarcinoma during surveillance (surveillance group). These patients had a histologically confirmed diagnosis of Barrett's oesophagus at least 6 months before surgery and had undergone at least one subsequent surveillance endoscopy. The second group included symptomatic patients whose initial presentation was with adenocarcinoma (non-surveillance group).

The frequency of endoscopic surveillance and the number of biopsies taken at each endoscopy varied during the study. In the first half, the time interval between endoscopies varied between 12 and 24 months, and there was no mandatory biopsy protocol. The number of biopsies obtained at each procedure was at the discretion of the individual endoscopist. From 1996 a stricter protocol was adopted, which included annual endoscopy and four quadrant biopsies at 2-cm intervals from the region of the lower oesophageal sphincter to the squamocolumnar junction[10].

Patients were considered for surgical resection if they had adenocarcinoma or unequivocal high-grade dysplasia on two successive endoscopies. Staging investigations included computed tomography of the chest and abdomen, and endoscopic ultrasonography in the latter part of the study. Pulmonary function tests, arterial blood gases and echocardiography were used to assess fitness for surgery. The majority of patients underwent radical Ivor–Lewis oesophagogastrectomy combined with two-field lymphadenectomy. A small number of patients underwent transhiatal or three-stage oesophagectomy in the early part of the study.

Resected tumours were staged according to the pathological tumour node metastasis (pTNM) classification of the Union Internacional Contra la Cancrum[25]. The presence of infiltration through the epithelial basement membrane was used to differentiate high-grade dysplasia from invasive adenocarcinoma. The term carcinoma *in situ* (pTis) was avoided; pT_1 tumours were further subclassified as pT_{1a} (confined to the mucosa) or pT_{1b} (infiltrating the submucosa).

Patients were seen every 3 months for the first year after surgery and every 6 months thereafter until death or the conclusion of the study. Follow-up included history and physical examination at each visit, and further investigations as indicated clinically. Survival data were collected from hospital records and cross-referenced with those held by general practitioners and the Yorkshire Cancer Registry.

Statistical analysis

Comparisons between groups were made by the Mann–Whitney *U* test and the χ^2 test. Overall survival rates were calculated by the method of Kaplan and Meier, and included operative mortality. Differences in survival between groups were assessed using the log rank test. The threshold of statistical significance was set at 0·050. Statistical analysis was performed using SPSS® 8·0 for Windows (SPSS, Chigago, Illinois, USA).

Results

One hundred and seventy-six consecutive resections were carried out for adenocarcinoma of the oesophagus or gastro-oesophageal junction. Ninety-one patients had associated Barrett's mucosa, of whom 17 (11 men, median age 70 years) had been under surveillance for a previous diagnosis of Barrett's oesophagus and 74 (61 men, median age 67 years) presented with symptomatic tumours. The two groups were similar with respect to age ($P = 0{\cdot}454$) and sex ($P = 0{\cdot}181$).

Patients in the surveillance group were known to have had histologically proven Barrett's epithelium for a median

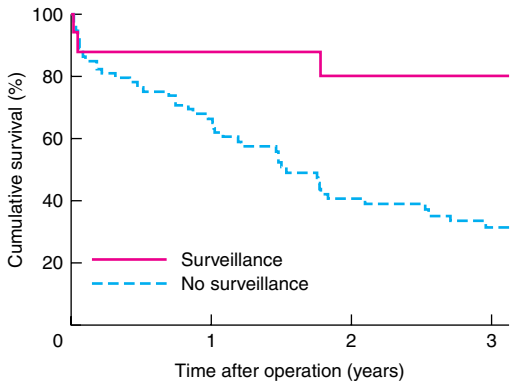
of 72 (range 6–123) months and had undergone a median of 4 (range 2–11) endoscopies before surgery. The median length of Barrett's segment at the final preoperative endoscopy was 8 (range 2–15) cm and a visible lesion was present in 12 of 17 patients. The indication for surgery was high-grade dysplasia in four and invasive adenocarcinoma in the remaining 13 patients. All patients in the non-surveillance group had a preoperative diagnosis of invasive adenocarcinoma.

Ivor–Lewis oesophagogastrectomy with two-field lymphadenectomy was carried out in 15 patients in the surveillance group and 61 patients in the non-surveillance group ($P = 0{\cdot}561$). However, the rate of complete (R_0) resection was higher in patients with surveillance-detected cancers (16 of 17 *versus* 42 of 74; d.f. $= 1$, $\chi^2 = 8{\cdot}35$, $P = 0{\cdot}004$).

Three of four patients in the surveillance group with a preoperative diagnosis of high-grade dysplasia had foci of invasive carcinoma. Of five patients with a preoperative diagnosis of cancer but no visible endoscopic lesion, one had a tumour that had reached the submucosa and had lymphatic metastases. The remaining six patients with submucosal lesions had no lymph node involvement.

Lymph node involvement was seen in three of 17 patients in the surveillance group and 42 of 74 in the non-surveillance group (d.f. $= 1$, $\chi^2 = 8{\cdot}46$, $P = 0{\cdot}004$). Tumours detected in the surveillance programme were at a significantly earlier stage: 13 of 17 *versus* 11 of 74 stage 0 or I, three *versus* 26 stage II, and one *versus* 37 stage III or IV (d.f. $= 2$, $\chi^2 = 27{\cdot}67$, $P < 0{\cdot}001$).

Two patients who had been under surveillance died after surgery and two died from recurrent disease at 21 and 44 months. Both patients who developed recurrence had relatively advanced tumours (T2 and T3) with lymphatic metastases. The remaining 13 patients were alive and free from disease at a median follow-up of 31 months. The operative mortality rate was similar in the surveillance and non-surveillance groups: two of 17 *versus* nine of 74 respectively. Overall survival was significantly better in patients who had surveillance: 88 *versus* 67 per cent at 1 year, and 80 *versus* 31 per cent at 3 years (log rank $= 7{\cdot}06$, $P = 0{\cdot}008$) (*Fig. 1*).



No. at risk

Surveillance	17	12	10	7
No surveillance	74	45	24	15

Fig. 1 Postoperative survival in patients who did or did not have endoscopic surveillance for Barrett's oesophagus

Discussion

In the current climate of evidence-based medicine, policy makers require confirmation that the risk of adenocarcinoma in patients with Barrett's oesophagus justifies the implementation of a costly surveillance programme to detect early and potentially curable malignancy. The results of the present study indicate that patients with surveillance-detected adenocarcinomas were diagnosed at an earlier pathological stage than those who presented with symptomatic tumours, and subsequent oesophageal resection resulted in significantly better survival. Surveillance thus improved clinical outcome, confirming the results of previous studies[26–28].

Patients with late irresectable tumours and those with locally advanced tumours who underwent preoperative chemoradiotherapy were excluded from this study because their disease could not be staged accurately. High-grade dysplasia is not universally accepted as an indication for oesophagectomy although, interestingly, three of the four patients with high-grade dysplasia eventually had a histological diagnosis of invasive adenocarcinoma. Exclusion of the patients with high-grade dysplasia did not affect the significance of the results.

Despite evidence that surveillance prolongs survival in patients with adenocarcinoma arising in Barrett's mucosa, controversy still exists with respect to the cost-effectiveness of such programmes. Several recent reports have addressed this issue. Provenzale *et al.*[21] used the Markov mathematical model to assess the cost-effectiveness of different strategies of surveillance (including no surveillance) in a computer cohort simulation of hypothetical patients with Barrett's oesophagus. Endoscopic surveillance every 5 years was the only strategy that had an incremental cost–utility ratio (a measure of cost-effectiveness) similar to that of other common medical practices such as mammographic screening for breast cancer. More frequent surveillance was more costly, yet yielded lower life expectancy. It should be emphasized that these calculations were based on certain assumptions about the natural history of Barrett's oesophagus, the diagnostic

accuracy of endoscopic biopsy protocols, morbidity and mortality rates associated with endoscopic and surgical procedures, and long-term survival after oesophagectomy. Published values for these parameters vary considerably and the applicability of the results of such a theoretical analysis to the clinical setting is uncertain. In addition, the assumptions were based on American epidemiology and significant adjustments may need to be made for the UK, where the prevalence of oesophageal adenocarcinoma is higher.

Three of 17 patients developed lymphatic metastases even though they underwent endoscopic surveillance every 12–24 months. Although the study was not designed to determine the optimum interval between endoscopies, these results indicate that surveillance every 5 years would have increased the number of interval cancers diagnosed at a more advanced stage. Furthermore, recent clinical studies based on existing surveillance programmes have demonstrated that endoscopic surveillance of Barrett's oesophagus compares favourably with screening mammography for the detection of early breast cancer and faecal occult blood testing for the detection of colonic cancer[8,29].

This was not a randomized clinical study and is therefore open to potential sources of bias[30,31]. Lag time bias (a longer apparent survival in surveyed patients owing to earlier detection of tumours rather than postponement of death) is unlikely to affect the results because differences in survival were analysed at the end of 3 years and the median survival of unselected patients with oesophageal cancer is approximately 18 months in most surgical series. The likelihood of length bias and pseudodisease bias (surveillance programmes tend to detect less aggressive or even non-aggressive tumours with intrinsically better prognosis) is small because invasive cancer was found in all but one patient in the surveillance group and the patients in the surveillance group were relatively young. Finally, selection bias (patients prepared to undergo surveillance are those who would have presented with earlier symptoms of cancer had they not been surveyed) is encountered in all surveillance programmes and is more difficult to refute. It is unlikely, however, that selection bias alone could explain the large differences in survival between the two groups in the present study. A prospective randomized trial would be required to demonstrate conclusively both the efficacy and cost-effectiveness of surveillance. Such an approach, however, would require thousands of patients with Barrett's oesophagus to be followed for many years[32,33]. In the light of existing evidence it may also be considered unethical to withhold a potentially life-saving procedure from patients with Barrett's oesophagus, even in the setting of a randomized trial.

The management of high-grade dysplasia in patients with Barrett's oesophagus remains controversial. Some authors claim that dysplasia can be differentiated from early adenocarcinoma if a rigorous systematic biopsy protocol is followed, and recommend continuing surveillance until invasive cancer is diagnosed[34,35]. The danger of this approach was illustrated in this series by the detection of foci of invasive adenocarcinoma in three of four patients with a preoperative diagnosis of high-grade dysplasia who underwent oesophagectomy. Several previous studies have reported similar findings[26,36,37]. Currently available imaging techniques cannot differentiate high-grade dysplasia from early cancer[38–40] and there is a risk of sampling error even with multiple biopsies from the abnormal mucosa. For this reason, the authors advocate surgical treatment for patients with unequivocal high-grade dysplasia on two successive endoscopies who are fit for surgery. The value of endoscopic fluorescence techniques in detecting early cancer in patients with high-grade dysplasia remains undetermined[41,42].

The implementation of surveillance programmes for patients with Barrett's oesophagus and a more liberal use of endoscopy in individuals with symptoms of reflux has led to an increasing number of patients being diagnosed with early oesophageal adenocarcinoma[16,43,44]. Several studies have shown that the incidence of regional lymph node metastasis correlates with the depth of invasion of the primary tumour[45–47]. Lymphatic spread is rare in patients with intramucosal carcinoma but this risk increases substantially when the tumour has penetrated to the submucosa or beyond. Consequently, the value of lymphadenectomy for cancers confined to the mucosa has been questioned and non-surgical techniques of ablation of the neoplastic mucosa, such as endoscopic mucosal resection and photodynamic therapy, have been advocated as alternatives to oesophagectomy[48–50]. However, accurate preoperative staging of T1 tumours is essential if such an approach is to be used. Currently available endoscopic ultrasound probes are not sufficiently sensitive to distinguish between intramucosal and submucosal tumours[51,52]. In the present study, 13 of the 17 patients in the surveillance programme had T1 tumours; seven were submucosal and one of these was node positive.

It has been suggested that the presence of an endoscopically visible lesion (ulcer or nodule) might be a reliable indicator of the depth of invasion of the tumour and that the type of operation can be tailored accordingly[53]. The findings of the present study do not support these observations. One of five patients without

a visible lesion in this series had a submucosal cancer with lymph node involvement. Oesophageal resection with adequate mediastinal and abdominal nodal clearance remains the treatment of choice for all patients with early carcinoma who are fit for major surgery. Complete removal of the metaplastic epithelium is also critical because a second carcinoma may develop in a residual Barrett's segment after incomplete resection[54]. The benefits of endoscopic surveillance of Barrett's oesophagus may be jeopardized if less radical and potentially inadequate treatment was offered to patients with early disease.

Regular endoscopic surveillance of patients with Barrett's oesophagus led to the detection of cancer at an early and potentially curable stage. Survival was improved compared with that of patients who presented with symptomatic tumours. Wider implementation of surveillance programmes may improve clinical outcome.

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