Oesophagectomy remains the gold standard for treatment of high-grade dysplasia in Barrett’s oesophagus

Vijay Sujendran *, Giuseppe Sica, Bryan Warren, Nicholas Maynard

Department of Upper GI Surgery and Pathology, The John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU, UK

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Abstract

Aim: The goal of surveillance in Barrett’s oesophagus is to detect high-grade dysplasia (HGD). The natural history of HGD is unclear, but because of the reported high risk of coexistent invasive carcinoma, oesophagectomy is currently the gold standard treatment. Recent reports suggest the risk of coexistent tumour may be lower and that the optimum treatment for HGD is continuing surveillance or mucosal ablation treatment, reserving oesophagectomy for those patients with invasive malignancy. To re-examine the role of oesophagectomy we looked at the incidence of invasive cancer in patients undergoing resection for HGD and their subsequent outcome. Methods: Prospective analysis of 240 patients undergoing oesophagectomy over 6 years under a single surgeon in a single centre. Analysis was focused on patients undergoing oesophagectomy for HGD picked up during Barrett’s surveillance endoscopy. The incidence of invasive cancer, morbidity, mortality and survival of this subgroup is reported. Results: Preoperatively, 17 patients were diagnosed with HGD and underwent oesophagectomy. Eleven of 17 (65%) patients had coexistent invasive cancer and six patients had HGD alone in the resected specimens. There was no in-patient mortality, four patients had significant respiratory complications and three patients had radiological/clinical anastomotic leaks. All 6 patients with HGD only are alive to date (3—68 months) and 3 of 11 patients with invasive cancer have died of recurrent disease. Conclusion: We continue to advocate oesophagectomy for HGD as the optimum treatment in the light of the high rate of coexistent invasive cancer. Oesophagectomy for HGD can be performed with low morbidity and minimal mortality in a specialist centre. We hypothesize that the lower rates of invasive cancer found in HGD reported by other groups result from interobserver variation in grading of HGD, variability in histological sampling of the resected oesophagus and variability in the endoscopic technique of acquisition of biopsy samples.

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1. Introduction

Over the past 30 years, the incidence of oesophageal adenocarcinoma has increased dramatically [1]. It has a regional variation, which is higher in our population in the UK compared to Europe, North America and the Far East. Adenocarcinoma of the oesophagus accounts for 70% of the oesophageal cancer in the UK and is the fifth leading cause of cancer mortality in our population (Cancer Research, UK). Gastroesophageal reflux disease is the major cause of adenocarcinoma of the gastro-oesophageal junction (GOJ) or distal oesophagus. Columnar-lined oesophagus (Barrett’s mucosa) is recognised as a premalignant lesion, leading to 30—125 times greater risk of adenocarcinoma than that in the general population [2]. The progression from intestinal metaplasia (IM) to low-grade dysplasia (LGD) to high-grade dysplasia (HGD) and finally to invasive carcinoma has been well described [2]. This process is thought to be driven by gastro-oesophageal reflux of acid and bile, probably influenced by genetic factors. Many clinicians now undertake routine surveillance of patients with Barrett’s oesophagus in an attempt to identify those who might benefit from treatment at a preinvasive stage of the disease. Many patients with HGD picked up on surveillance endoscopy will either already have a focus of carcinoma or will shortly develop invasive disease [3—5], and for this reason many centres now advocate oesophagectomy for HGD [3,4]. There is, however, a wide variation in the reported incidence of carcinoma in oesophagectomy specimens from patients undergoing surgery for HGD, from 0 to 73% [4—6]. There are three possible explanations for this wide variation: the number and size of endoscopic biopsies [7], interpathologist variations in the reporting of what constitutes HGD versus LGD [5,8] and the intensity of the search for the foci of invasive tumour in oesophagectomy specimens [5]. Centres with low incidences of invasive cancer advocate continuing aggressive surveillance for HGD, reserving oesophagectomy for invasive malignancy [9—11]. There remains an ongoing
debate about the optimum management of high-grade dysplasia arising within Barrett’s oesophagus.

2. Methods

We prospectively gathered data of patients undergoing oesophagectomy over 6 years under a single surgeon in a single centre. Analysis was focused on patients undergoing oesophagectomy for HGD picked up on Barrett’s surveillance endoscopy. Data collected included age, sex, diagnosis, clinical presentation, type of surgical procedure, intensive care stay, in-hospital stay, major and minor complications, anastomotic leak, histopathological analyses preresection and postresection, development of locoregional recurrence or distant metastases, last follow-up and cause of death.

2.1. Biopsy protocol

During routine surveillance endoscopies we took quad-rantic biopsies with jumbo forceps from every 2 cm of columnar lined oesophagus (CLO) and targeted biopsies of any visible lesions within the area of Barrett’s oesophagus. When dysplasia was known to be present, we took quadrantic biopsies from every 1 cm of CLO and targeted biopsies of any lesions. Any diagnosis of HGD was confirmed by two experienced independent histopathologists; the patient was treated with a therapeutic dose of a proton pump inhibitor, and repeat biopsies were taken 6 weeks later to confirm the presence of HGD. Once HGD was confirmed, endoscopic ultrasound scan (EUS) was then carried out and further biopsies were taken of any lesions previously unrecognised. This is because in our centre patients with T2 and T3 cancer undergo neoadjuvant chemotherapy and therefore patients with initial diagnosis of HGD undergo EUS to assess the T stage in order to identify any potential patients who might require neoadjuvant chemotherapy.

2.2. Definition of HGD

The following features were observed by both pathologists in order to make the diagnosis of high-grade dysplasia.

(1) Distorted/irregular growth pattern of the glands or rows of cells.
(2) Severe cytological and architectural abnormalities.
(3) Branching or budding of glands.
(4) Distortion of glandular architecture at low power. This may be marked and may be composed of branching and lateral budding of crypts, a villiform configuration of the mucosal surface, or intra-glandular bridging of epithelium to form a cribriform pattern of ‘back-to-back’ glands.
(5) More than 50% of the cells have large nuclei and are frequently dividing.
(6) The number of goblet cells is reduced.
(7) The nucleus-to-cytoplasm ratio is increased.

Dysplastic epithelium extends onto the mucosal surface with loss of nuclear polarity, characterized by the ‘rounding up’ of the nuclei and absence of a consistent relationship of nuclei to each other.

2.3. Data analysis

The following parameters were analysed: the incidence of invasive cancer and HGD in the resected specimen, TNM staging, postoperative complications, intensive care stay, in-hospital stay, in-hospital mortality, disease recurrence and overall survival.

A Kaplan—Meier survival curve was used to compare the differences in outcome for patients with a final histopathological diagnosis of HGD against those with coexistent invasive carcinoma.

3. Results

Of the total of 17 patients who underwent oesophagectomy 15 were males and 2 females with a median age of 62 years (53—74 years). Sixteen patients underwent trans-hiatal oesophagectomy and one patient underwent Ivor—Lewis oesophagectomy (previously trans-thoracic and trans-abdominal anti-reflux procedures). The median intensive care stay was 1 day (1—7 days). Sixteen patients spent only 1 day in intensive care, while one patient who developed acute lung injury stayed for 7 days. The median in-hospital stay was 11 days (9—26 days). Further, three patients developed postoperative pneumonia requiring treatment. Two patients had a radiological anastomotic leak and one patient had a clinical leak that was managed conservatively. There was no in-patient mortality.

In 6 of the surgical specimens there was HGD alone, whereas in 11 surgical specimens there were foci of invasive malignancy. Pathological staging of the 11 invasive cancers were as follows: T1N0—9, T2N0—1 and T1N1—1. There was no positive longitudinal or circumferential margin involvement in any of the specimens. The median harvest of lymph nodes in specimens positive for invasive tumours was 9 [3—16].

3.1. Survival

All 17 patients have been followed up (median 32 months, range of 3—68 months). All six patients with HGD alone are alive to date. Of the 11 patients with invasive cancer, 3 developed recurrent disease at 24, 36 and 43 months following initial operation (see Fig. 1), and all have died.

Fig. 1. Kaplan—Meier survival graph comparing HGD to T1a, T1b and T2.
4. Discussion

The stepwise progression from intestinal metaplasia to low-grade dysplasia to high-grade dysplasia to carcinoma in the columnar-lined oesophagus has been well described. Hameeteman et al. [12] prospectively followed 50 patients with Barrett’s oesophagus over a period of 1.5–14 years with a mean of 5.2 years. They showed a clear sequential progression of worsening dysplasia leading to the development of invasive carcinoma. Three patients developed high-grade dysplasia and further five patients developed adenocarcinoma. The study population had a 125-fold increased risk of developing oesophageal adenocarcinoma compared to the general population in Holland. Weston et al. [13] prospectively followed 108 patients with Barrett’s oesophagus with a follow-up ranging from 12 to 101 months (mean 39.9; SD 20.8). Five patients developed multifocal HGD and further five patients developed invasive cancer.

The reported incidence of invasive cancer in oesophagectomy specimens following oesophagectomy for HGD varies from 0 to 73% [4—6]. The true incidence of invasive carcinoma is uncertain and interpretation of these reports is complicated by several factors: there is variable practice among endoscopists regarding the appropriate number and size of biopsies; there is an interobserver error amongst pathologists in the diagnosis of HGD, leading to a risk of over-diagnosis of HGD; small foci of invasive cancer in the final oesophageal specimen may be missed. Cameron and Carpenter [5] histologically mapped oesophagectomy specimens from patients undergoing oesophagectomy for either HGD or early adenocarcinoma. They demonstrated that areas of microscopic carcinoma are often extremely small and can easily be missed; the median surface area of adenocarcinoma was only 3% of the total Barrett’s oesophagus surface area. Falk et al. [7] showed that even when using jumbo biopsy forceps the foci of invasive carcinoma can still be missed in 33% of patients with HGD, and indeed the jumbo biopsy forceps were no better than standard endoscopic biopsy forceps in this regard. Peters et al. [14] showed that even with repeated endoscopy and aggressive biopsy of the Barrett’s mucosa (median of 7.8 biopsies per 2 cm of Barrett’s mucosa) invasive carcinoma was missed in 56% of patients with HGD.

We have seen 17 patients with HGD within Barrett’s oesophagus. We work in a tertiary referral centre, and therefore some of these patients are referred from other hospitals in our Cancer Network. Consequently we know neither the total number of patients undergoing Barrett’s surveillance nor the length of time the referred patients had been surveyed. All referred patients had repeat biopsies carried out in our Unit according to the protocol mentioned above. All patients were fully counselled and offered oesophagectomy. No patient refused and therefore all patients seen in our Unit with HGD arising in Barrett’s oesophagus underwent oesophagectomy. Eleven patients (65%) had invasive cancer in the final surgical specimen. We believe the main reason for this high rate of coexistent cancer is a more rigorous and objective definition of HGD and the requirement for a consensus between two independent pathologists. Skacel et al. [15] demonstrated a high degree of interobserver variability in the histological diagnosis of dysplastic Barrett’s oesophagus but did comment that when there was a consensus amongst pathologists on the diagnosis of LGD the risk of progression to HGD or carcinoma was much higher. Furthermore, we believe our detailed and aggressive analysis of the surgical specimen picks up small foci of invasive carcinoma, which may otherwise be missed. In our practice, multiple areas of Barrett’s oesophagus were block dissected at 2–3 mm and if HGD was present, the specimen was further block dissected at three levels to exclude T1a and T1b invasion. The increasing use of endoscopic ultrasound sonography (EUS) may pick up small lesions not diagnosed at normal endoscopy, thus enabling further targeted biopsies. Nevertheless, EUS is unlikely to pick up lesions less than 3–5 mm [16].

Certain centres recommend aggressive endoscopic surveillance, and not oesophagectomy, for HGD. Levine et al. [17], using a rigorous systematic endoscopic biopsy protocol, demonstrated 100% accuracy in the preoperative endoscopic diagnosis of HGD without associated adenocarcinoma when compared to the eventual surgical specimen and suggested that continuing endoscopic surveillance was appropriate for patients with HGD. However, the diagnoses of HGD were made by one pathologist only, and their conclusions were based on only seven patients with HGD. Furthermore, their aggressive biopsy protocol would not be feasible in most institutions (some patients had more than 10 biopsies per cm of Barrett’s mucosa).

Recently, non-surgical approaches such as endoscopic mucosal ablation or mucosal resection have attracted increasing interest in the treatment of Barrett’s HGD. Mucosal ablation therapies using photodynamic therapy, argon beam photocoagulation or thermal ablation are being used predominantly in research studies [18,19], and concerns increase about residual intestinal metaplasia persisting deep to the new squamous epithelium. Indeed, there have been some worrying reports of adenocarcinoma developing in buried columnar epithelium [18]. Randomized controlled trials of mucosal ablation therapy are awaited. Endoscopic mucosal resection [20] shows much promise and may well become the treatment of choice for superficial lesions and short segments of dysplastic columnar epithelium. Its role in longer segments of Barrett’s mucosa remains unclear.

We, as also others, have shown that most patients with an endoscopic diagnosis of HGD will already have a focus of invasive carcinoma. Even if invasive carcinoma is not present, the rapidity with which HGD develops into invasive malignancy is variable and unpredictable and can be alarmingly quick [12]. Oesophagectomy remains an operation associated with significant morbidity and mortality, and for HGD arising in short segments of CLO, it may be appropriate to perform a limited resection of the distal oesophagus and oesophago gastric junction with reconstruction by interposition of an isoperistaltic pedicled jejunal segment (Merendino procedure [21]). It is possible that non-surgical techniques for ablating or removing dysplastic epithelium may one day reduce the need for surgical resection, but at present, however, surgical resection remains the only reliable means of curing HGD, and we believe there is nothing to be gained by waiting until invasive malignancy has developed, which will inevitably lead to a reduction in long-term survival. It is our opinion that oesophagectomy, carried out in a specialist unit...
with a low mortality rate, is the optimum treatment for Barrett’s HGD in patients of acceptable age and comorbidity.

References


