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REVIEW

Operable gastro-oesophageal junctional adenocarcinoma: Where to next?

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Abstract

Oesophageal junctional adenocarcinoma is a challenging and increasingly common disease. Optimisation of pre-operative staging and consolidation of surgery in large volume centres have improved outcomes, however the preferred adjunctive treatment approach remains a matter of debate. This review examines the benefits of neoadjuvant, peri-operative, and post-operative chemotherapy and chemoradiotherapy in this setting in an attempt to reach an evidence based conclusion. Recent findings relating to the molecular characterisation of oesophagogastric cancer and their impact on therapeutics are explored, in addition to the potential benefits of fluoro-deoxyglucose positron emission tomography (FDG-PET) directed therapy. Finally, efforts to decrease the incidence of junctional adenocarcinoma using early intervention in Barrett's oesophagus are discussed, including the roles of screening, endoscopic mucosal resection, ablative therapies and chemoprevention.

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Key words: Oesophageal adenocarcinoma; Junctional adenocarcinoma; Gastric adenocarcinoma; Peri-operative chemotherapy; Pre-operative chemoradiotherapy; Molecular profiling; Fluoro-deoxyglucose-positron emission tomography; Barrett's oesophagus; Chemoprevention

Core tip: Cancer of the gastro-oesophageal junction is an increasingly common phenomenon. For patients with operable junctional cancer, the only curative treatment option is surgery, however the optimal peri-operative treatment is controversial. We review the evidence supporting the use of chemotherapy and chemoradiotherapy in the pre- and postoperative settings for these patients, and go on to highlight how current research into the molecular mechanisms underpinning gastro-oesophageal cancer may lead to future effective treatment options.

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INTRODUCTION

Adenocarcinoma of the oesophagogastric junction presents an increasingly common dilemma in many affluent countries, and the optimal treatment approach for patients with resectable disease is a matter of some controversy[1]. In addition to surgery for their cancer, and depending on geographical location and physician preference patients may undergo neoadjuvant, peri-operative, or post-operative chemotherapy, or pre- or post-operative chemoradiotherapy[2-4]. Unfortunately, despite improvements in staging and patient selection, long term survival following resection remains relatively poor and further refinement of treatment paradigms and novel therapeutic interventions are required. This aim of this review is to assess the current status of our knowledge on tumours of the gastroesophageal junction with respect to tumour

Table 1 Selected trials of peri-operative therapy for junctional oesophageal adenocarcinoma

Trial	Year	% Junctional adenocarcinoma or lower oesophageal tumours	*n*	Treatment	Survival (%)
Peri-operative chemotherapy					
MAGIC[5]	2006	Adenocarcinoma 100%	503	Surgery	23.00
		Lower oesophageal/GEJ 26%		Peri-operative chemotherapy	36.30 (5-year-OS)
FNCLCC-FFCD[6]	2011	Adenocarcinoma 100%	224	Surgery	24
		Lower oesophagus 11%, GEJ 64%		Peri-operative chemotherapy	38 (5-year-OS)
OEO2[7,8]	2009	Adenocarcinoma 66.5%	802	Surgery	17.10
		Lower 1/3 and cardia 75%		Neoadjuvant chemotherapy	23.00 (5-year-OS)
Pre-operative chemoradiotherapy					
Stahl[13]	2009	Adenocarcinoma 100%	126	Neoadjuvant chemotherapy	27.70
		GEJ 100%		Neoadjuvant chemoradiotherapy	47.40 (3-year-OS)
Tepper[14]	2009	Adenocarcinoma 75%	56	Surgery	1.79y
		Distal oesophagus/GEJ 100%		Neoadjuvant chemoradiotherapy	4.48y (median OS)
CROSS[15]	2012	Adenocarcinoma 74%	366	Surgery	44
		Distal 1/3 oesophagus 57, GEJ 24%		Neoadjuvant chemoradiotherapy	58 (3-year-OS)
Post-operative chemoradiotherapy					
INT-0116[16]	2001	Adenocarcinoma 100%	556	Surgery	41
		Cardia 20%		Adjuvant chemoradiotherapy	50 (3-year-OS)

DFS: Disease free survival; GEJ: Gastroesophageal junction; OS: Overall survival; SCC: Squamous cell carcinoma.

biology and therapy and to examine how developments in targeted therapy, radiotherapy, screening, and chemoprevention may improve outcomes for patients with this disease.

PERI-OPERATIVE CHEMOTHERAPY

In Western populations, many patients presenting with junctional adenocarcinoma have relatively locally advanced disease at presentation, and whilst there may be debate regarding the optimal treatment approach, there is agreement that something more than surgery is required to increase survival (Table 1). In Europe and selected United States academic centres, peri-operative chemotherapy is the treatment of choice for these patients. This choice is based on the United Kingdom MRC MAGIC trial, which treated over 500 patients with stomach, junctional or oesophageal tumours to either surgery alone or surgery plus peri-operative chemotherapy with epirubicin, cisplatin and 5-fluorouracil (5-FU)[5]. Peri-operative chemotherapy led to a 37% reduction in the risk of progression following surgical resection and improved 5 year survival from 23% in the surgery alone arm to 36% in those treated with chemotherapy (HR = 0.75, 95%CI: 0.60-0.93; $P = 0.009$). In MAGIC one quarter of patients had tumours of the gastroesophageal junction (GEJ) or lower oesophagus and subgroup analysis demonstrates that the greatest benefit was seen in patients with junctional tumours. These results are supported by the results of the randomised phase Ⅲ FNCLCC/FFCD French study in which 224 patients were randomised to surgery alone or peri-operative cisplatin and 5-fluorouracil chemotherapy[6]. The results from this study (in which 75% of patients had junctional tumours) are remarkably similar to those seen in MAGIC, with an improvement in 5 year overall survival from 24% to 38% (HR = 0.69, $P = 0.02$) for the interventional arm.

The aim of peri-operative chemotherapy is two-fold; firstly to downstage the primary tumour with a view to obtaining an R0 resection, and secondly to treat occult micro-metastatic disease. The neoadjuvant component of both MAGIC and the French study improved curative resection rates for patients in both these trials, in MAGIC 79.3% of chemotherapy patients were curatively resected compared to 70.3% in the surgery alone arm ($P = 0.03$), these figures are 84% and 73% respectively for the FFCD trial ($P = 0.04$). That subclinical micrometastases are eliminated is demonstrated by the almost uniform 35%-37% reduction in disease recurrence which seen across the two studies.

NEO-ADJUVANT CHEMOTHERAPY ALONE: IS IT ENOUGH?

Interestingly, a neo-adjuvant chemotherapy alone approach (with no post-operative component) does not appear to provide the same benefit to patients with oesophagogastric cancer. In the MRC OE02 study 802 patients with primarily oesophageal cancer (two thirds adenocarcinoma) were randomised to surgery alone or 2 cycles of cisplatin and 5-FU prior to surgery[7,8]. Although this study did demonstrate a survival benefit for patients treated with chemotherapy regardless of histology (5 year survival 23% *vs* 17%, $P = 0.03$), these results are not consistent with the results of the RTOG 8911 trial ($n = 467$) in which no difference was seen in the survival outcomes for a similar group patients treated with pre-operative chemotherapy[9]. Consistent with the negative results of the RTOG 8911 study are those of the smaller EORTC 40954 trial ($n = 144$, of whom half were junctional tumours). This study demonstrated an increase in the R0 resection rate following pre-operative cisplatin and 5-FU chemotherapy, but no improvement in overall survival[10]. These somewhat heterogeneous results have been combined in a meta-analysis which did demonstrate an improvement in survival for the neoadjuvant chemotherapy approach (HR = 0.90 for neoadjuvant chemotherapy, 95%CI: 0.81-1.00, $P = 0.05$)[11]. The benefit seen

appears to be due to the adenocarcinoma population (HR = 0.78, P = 0.014) as no significant difference was seen in the squamous cell carcinoma analysis. Therefore, although neoadjuvant chemotherapy alone for junctional tumours is not as clearly advantageous as treatment given both pre- and post-operatively, it is a reasonable choice if patients cannot tolerate post-operative chemotherapy.

NEOADJUVANT CHEMORADIOTHERAPY: DOES MAXIMISING LOCAL CONTROL LEAD TO IMPROVED SURVIVAL?

Response rates to radiotherapy are high, and if tumour downstaging in order to improve operative outcomes is the aim of therapy then radiotherapy has clearly defined benefits. However, if long term survival is the goal of treatment, many studies in junctional adenocarcinoma provide conflicting results. Analysis of the results of these studies must be careful, with consideration given to the external validity or generalizability of the data presented. Many trials present results based on both squamous cell carcinoma and adenocarcinoma patients between whom there are clear biological differences. Squamous cell carcinoma is exquisitely radiosensitive and may not require surgical resection if a pathological complete response is obtained following chemoradiotherapy. Adenocarcinoma is less likely to demonstrate such a response and will always require surgery in order to maximise the chance of long term survival. As such, caution must be used when extrapolating results from clinical trials as whole to biologically distinct patient groups.

Older studies of chemoradiotherapy for junctional cancers demonstrate mixed results. One of the first trials of neo-adjuvant cisplatin/5-FU based chemoradiotherapy for junctional type adenocarcinoma demonstrated a significant increase in survival for patients treated with combined modality therapy compared to those treated with surgery alone (16 m *vs* 11 m, P = 0.01)[12]. However, interpretation of these results should be made with care as this trial was small (n = 58), patients underwent limited staging by current standards (CXR and abdominal ultrasound only), and survival was poor in the control arm of the study. Following this two other small studies also demonstrated a benefit to this combined modality approach; the POET study randomised 126 patients with junctional adenocarcinoma to pre-operative chemotherapy and surgery or to induction chemotherapy followed by chemoradiotherapy and then surgery[13]. Survival was numerically improved by the addition of chemoradiotherapy (3 year survival 47% *vs* 28%, P = 0.07), but the study was underpowered due to low accrual and this did not reach statistical significance. CALGB 9781 (75% adenocarcinoma) also utilized a tri-modality approach in its experimental arm and demonstrated statistically superior survival for chemoradiotherapy when compared to surgery alone [Overall survival (OS) 4.5 years *vs* 1.8 years, P = 0.002], however the small number of patients in this trial (n = 56) and the lack of histological subgroup analysis limit interpretation of these interesting results[14].

The publication of the phase Ⅲ randomised CROSS trial which compared chemoradiotherapy (weekly carboplatin and paclitaxel with 41.4 Gy radiotherapy in 23 fractions over 5 wk) to surgery alone have lead to a paradigm shift in the treatment of junctional cancers in many institutions[15]. Three hundred and sixty six patients with oesophageal cancer (75% adenocarcinoma, 23% squamous cell carcinoma, 2% undifferentiated) were randomised, of whom the majority had tumours of the distal oesophagus (58%) or gastroesophageal junction (24%). Overall survival results for chemoradiotherapy in CROSS are compelling; survival was 24 mo for surgery alone compared to 49 mo for chemoradiotherapy (HR = 0.67, P = 0.003). However, several caveats apply. Firstly, the control arm in CROSS was surgery alone and the benefits of chemoradiotherapy compared to a contemporary control such as neoadjuvant chemotherapy are unknown. Secondly, in the adjusted survival analysis, the benefit of combination therapy is not significant for adenocarcinoma patients (P = 0.07), providing evidence that the overall results for the study were driven by the radiosensitivity of the squamous cell carcinoma patient population.

Chemoradiotherapy provides a clear advantage over chemotherapy alone in terms of pathological complete response and local recurrence. In CROSS 29% of patients overall demonstrated a complete response, however this was much more common in squamous cell cancers (49%) than in adenocarcinoma (23%). It is worth noting however, that although pathological complete response is an attractive endpoint, it is not necessary in order to achieve either tumour downstaging or an R0 resection, and that peri-operative chemotherapy alone can help to achieve both these endpoints as demonstrated in FNCLCC/FFCD and MAGIC[5,6]. Patients with junctional adenocarcinoma are also much more likely to harbour systemic micro-metastatic disease, and there is some concern that the systemic chemotherapy dose in CROSS is insufficient to eliminate these. This concern is highlighted by the fact that patients in CROSS with N1 or greater staging at presentation did not appear to benefit from chemoradiotherapy in the adjusted survival analysis (P = 0.21), implying that those at high risk of systemic relapse require a higher dose of systemic therapy in addition to an effective local treatment. Ultimately, there is no doubt that chemoradiotherapy is an excellent and frequently curative treatment for squamous cell carcinoma, and perhaps for very early node negative adenocarcinoma, but for patients with more locally advanced disease (who comprise the majority of patients seen), the evidence is less robust. A clinical trial comparing pre-operative chemoradiotherapy to peri-operative chemotherapy is underway (NCT01726452) and may in time give clarification to this important issue.

POST-OPERATIVE ADJUVANT CHEMORADIOTHERAPY

Post-operative adjuvant chemoradiotherapy is a strategy

more often adopted for resected gastric cancers in the United States[16]. In the landmark INT0116 study 556 patients were randomised to no treatment following surgery or to chemoradiotherapy consisting of 45 Gy with fluorouracil and leucovorin on a Mayo-type regimen schedule. A recently published 10 year follow up of this study demonstrated a long term survival benefit -50% of patients treated with chemoradiotherapy survived for five years, compared to 41% who received no further treatment with a 51% reduction in the risk of recurrence and a 32% reduction in the risk of death attributable to the interventional arm[17]. Although the majority (80%) of patients in the Intergroup study had true stomach cancers, approximately 20% had junctional adenocarcinoma, and for patients who have not undergone pre-operative treatment, this remains an evidence based treatment option. Of significant concern is the fact that most patients in this study did not have an adequate surgical resection (although this is more significant for gastric patients as opposed to oesophageal), and therefore radiotherapy in the post operative setting may merely compensate for insufficient surgery. A second problem with adjuvant chemoradiotherapy relates to tolerability; post-operative morbidity associated with gastrectomy is significant, and preoperative therapy tends to be much more tolerable to patients than post-operative. For example, in MAGIC and the FNCLCC/FFCD trials of peri-operative chemotherapy more than 85% of patients completed the neoadjuvant component of therapy, compared to less than 50% who complete the post-operative treatment[5,6]. Furthermore, as many patients with junctional adenocarcinoma have relatively bulky tumours which benefit from downstaging withholding therapy until the post-operative period may disadvantage the patient if attempting to achieve a curative R0 resection. Finally, although adjuvant chemotherapy alone as used in the ACTS-GC and CLASSIC studies provides a well defined survival benefit, these trials were almost completely composed of patients with resected gastric cancer, not junctional cancers, and also conducted in Asian populations with distinct surgical patterns and pharmacogenomic profiles[4,18]. For these reason, we prefer a pre-operative treatment approach for most patients with junctional adenocarcinoma if this is possible.

STRATEGIES TO IMPROVE OUTCOMES: NOVEL TARGETS, IMAGING AND EARLY INTERVENTION

Understanding disease biology leads to new targets for drug development

Despite the fact that oesophagogastric cancer is most prevalent in the affluent West and frequently in patients of higher socioeconomic status, survival remains mediocre. Although neoadjuvant or peri-operative therapy improves survival by over one third, relapse is common[5,6,15]. Interval improvement in outcomes have been due to stage migration which occurs as a result of improved staging, routine use of pre-operative positron emission tomography-computed tomography (PET-CT) and laparoscopy (in particular for patients with type Ⅲ tumours) may prevent futile surgery in up to one fifth of patients[19]. In order to build on these gains, it will be necessary to exploit the biology of the disease with changes in treatment approach to targeted drugs and/or immunotherapies, strategies which have yielded immense returns in other malignancies such as melanoma[20-22]. Although gastroesophageal cancer is currently treated as a single disease entity, this designation is based on anatomy, not biology and in future treatment paradigms may differ according to the underlying dysregulated molecular characteristics rather than the spatial location. From an epidemiological perspective, lower oesophageal and junctional cancers have a distinct set of risk factors, quite separate from distal gastric cancer. Whereas antral cancers are endemic in high risk areas, strongly correlated with *Helicobacter pylori* (*H. pylori*) infection, associated with poor diet and high salt intake, proximal cancers do not appear to be related to *H. pylori*, but are associated with obesity and chronic reflux oesophagitis[23-26]. Despite these differences, junctional and distal tumours both progress through a predictable path of histological changes en route to a Lauren's intestinal cancer phenotype and display similar biological behaviours. Ultimately junctional and distal cancers are more similar in nature to each other than to diffuse gastric cancer, a disease which when non-hereditary has no known epidemiological risk factors or precursor lesions, and which has a characteristic pattern of infiltrative peritoneal spread[27,28].

Molecular characterisation of gastric cancer has moved forward in recent years, with several groups attempting to define molecular signatures which may correlate with Lauren's pathological classification, provide information on prognosis or predict response to chemotherapy[29,30]. To date these approaches remain exploratory and require further validation in larger patient cohorts. Genome wide sequencing approaches have failed to identify many any significant driver mutations in oesophagogastric cancer; mutation rates in most well known oncogenes such as *BRAF*, *KRAS* and *PIK3CA* are relatively low and therefore it is difficult to determine whether they are associated with prognosis or response to chemotherapy[31,32]. Interestingly, in one study specifically exploring the genomic landscape of junctional adenocarcinoma almost half (49%) of recurrently mutated genes were unique to this tumour subsite when compared to previously reported mutations in gastric cancer[33]. Mutations are more frequent in key tumour suppressor genes such as *p53* and *ARID1A*, but unfortunately these are currently more difficult to exploit therapeutically, although potentially actionable activating mutations have also been documented in genes such as *FGFR4* and *HGF*[32,33]. Outside the spectrum of activating driver mutations, a significant proportion of gastroesophageal cancers demonstrate predominantly mutually exclusive amplification of receptor tyrosine kinases which may be targeted successfully with novel agents[34]. Over one third of cancers demonstrate amplification of one of *ERBB2*, *MET*, *FGFR*, *KRAS* or *EGFR*, and while it

appears that these cancers may be more clinically aggressive, they may also potentially benefit from treatment with novel targeted drugs[34-36].

Trastuzumab, the monoclonal antibody targeting the human epidermal growth factor receptor 2 (HER-2) receptor tyrosine kinase, was the first targeted therapy do demonstrate efficacy in oesophagogastric cancer, with an improvement in median overall survival to an unprecedented 16 mo for patients with advanced HER2 immunohistochemistry (IHC)3+ or IHC2+ fluorescence *in situ* hybridisation (FISH) positive tumours treated with chemotherapy plus trastuzumab[37]. This compares very favourably to median survival for similar patients treated with standard chemotherapy regimens which is generally less than one year[38,39]. In breast cancer, trastuzumab is associated with increased response rates and improved surgical outcomes when administered neoadjuvantly, and is curative in the adjuvant setting[40,41]. It is therefore a matter of regret that no registration study for trastuzumab was performed in conjunction with peri-operative chemotherapy for resectable gastroesophageal cancer, where up to 25% of patients with junctional cancers (who overexpress HER-2) could benefit[42]. However, for those who prefer a trimodality approach, a United States study will assess the benefits of the addition of trastuzumab to a CROSS like regimen of chemoradiotherapy for patients with resectable HER-2 positive oesophageal cancer (NCT01196390). The addition of pertuzumab (the monoclonal antibody inhibitor of HER-2 dimerization) to trastuzumab therapy has led to significant gains in overall survival for patients with metastatic breast cancer, as has the anti-HER2 antibody drug conjugate TDM1, and both pertuzumab (NCT01774786) and TDM1 (NCT01641939) are currently being evaluated in large, international randomised trials in HER2 positive gastric cancer in the first and second line setting respectively[43]. Therefore in future it is hoped it that these may play a role in the peri-operative setting.

Other potential pathways of interest for patients with gastroesophageal cancer include targeting angiogenesis, MET and fibroblast growth factor receptor (FGFR). Therapies targeting MET and FGFR, although promising from a preclinical perspective, have limited clinical evidence for efficacy at this stage beyond anecdotal reports from early phase clinical trials. However, there is substantial evidence to support an anti-angiogenic approach in operable gastroesophageal cancer. In a placebo controlled phase Ⅲ randomised trial the anti-VEGFR2 antibody ramicurumab led to a significant improvement in survival compared to best supportive care in previously treated advanced gastric cancer (OS 5.2 m *vs* 3.8 m HR = 0.78, $P = 0.047$)[44]. Interestingly, the benefit seen in terms of overall survival was comparable to that demonstrated in randomised studies of cytotoxic therapies in the same setting[45]. Ramicurumab has also improved survival when added to paclitaxel in the second line setting resulting in a median overall survival of an unprecedented 9.63 m for previously treated patients (HR = 0.807, 95%CI: 0.678-0.962; $P = 0.0169$)[46]. Furthermore, although in the phase Ⅲ randomised AVAGAST study for patients with advanced gastric cancer the addition of bevacizumab to cisplatin-fluoropyrimidine chemotherapy did not lead to a benefit in terms of overall survival, significant improvements in response rate and progression free survival were seen in the experimental arm[47]. As the goal of therapy in the peri-operative setting is to maximise response rate in order to achieve an R0 resection, then the addition of bevacizumab to peri-operative chemotherapy would appear to be a rational choice. This approach has been adopted in the large United Kingdom MRC ST03 trial, which will evaluate the addition of bevacizumab to peri-operative epirubicin, cisplatin and capecitabine chemotherapy (NCT00450203). This study completed recruitment of over one thousand patients in late 2013 and preliminary results are expected within the next two years.

IMAGE DIRECTED THERAPY: LARGER PATIENT COHORTS ARE NEEDED TO VALIDATE THIS PROMISING BIOMARKER

The routine use of PET-CT is helpful in staging patients with potentially operable junctional adenocarcinoma and may decrease the rate of futile surgery by identifying patients with CT-occult metastatic disease[19]. PET-CT has the potential to become a useful tool in assessing early response to treatment in oesophagogastric cancer, however studies evaluating this as a predictor of response have been small and lack validation. In the MUNICON I study of 54 patients with oesophageal cancer who failed to demonstrate a metabolic response following one cycle neoadjuvant chemotherapy (defined as ⩽ 35% decrease in SUV) no patient had a histological response and median survival for these patients was significantly worse than those who had a metabolic response (HR = 2.18, 95%CI: 1.32-3.62, $P = 0.002$)[48]. In the follow up MUNICON Ⅱ study patients who failed to demonstrate a metabolic (PET) response to a single cycle of pre-operative chemotherapy were treated with salvage chemoradiotherapy[49]. Although this did increase the pathological response rate compared to chemotherapy alone in the previous study it did not improve the R0 resection rate, and PET-non responders had almost half the rate of 2 year progression free survival of metabolic responders (64% for PET responders and 33% for PET non-responders (HR = 2.22, $P = 0.035$), highlighting the aggressive disease biology of non-responding patients. Unfortunately despite these intriguing findings the small number of patients in the MUNICON studies preclude these changing clinical practice and larger clinical trials will be required in order to do this; the CALGB group have initiated a study in which over two hundred patients with junctional adenocarcinoma are randomised induction chemotherapy with either FOLFOX (oxaliplatin plus fluorouracil) or carboplatin and paclitaxel with interval PET being performed following three cycles of treatment (NCT01333033). Patients who fail to respond on PET (⩽ 35% reduction in SUV) will cross over to the alternate treatment arm

of the study for concurrent chemoradiotherapy. The primary endpoint of this study is to increase the rate of pathological complete response in the initial PET non-responders to 20%, with progression free and overall survival being secondary endpoints. The UK MRC ST03 study (NCT00450203) which is evaluating the addition of bevacizumab to peri-operative chemotherapy is also performing a PET substudy which may provide further important information on this topic.

DECREASING CANCER RELATED MORTALITY WITH EARLY INTERVENTION

By the time symptoms such as dysphagia become apparent for patients with junctional adenocarcinoma the disease is often well established and frequently not amenable to surgery. Additionally, for those who are suitable for an operative approach the morbidity associated with such invasive surgery and peri-operative therapy is such that many patients may be excluded from curative treatment due to co-morbidity or performance status. However, for the small number of patients who are diagnosed with early stage cancers endoscopic resection may provide comparable results to surgical resection with less morbidity[50,51]. For patients with intramucosal carcinoma or high grade dysplasia with visible lesions endoscopic resection in a high volume centre is recommended with subsequent management dictated by the depth of tumour invasion on pathology[52]. Radiofrequency ablation is recommended for patients with early cancer or high grade dysplasia with no visible lesions/flat lining and for complete eradication of residual visible Barrett's oesophagus following endoscopic mucosal resection[51-55]. Based on randomised trial data, endoscopic resection of the entire Barrett's mucosa does not appear to provide any increased benefit over endoscopic resection of only visible lesions and radiofrequency ablation of the remainder of visible areas of Barrett's[56]. The case for endoscopic intervention is less clear for patients with low grade dysplasia, although there is clear evidence that ablative therapies can eradicate low grade dysplasia, given the low incidence of progression of such lesions to overt malignancy the benefit of this approach to patients is not definitively proved[52,57-60]. A randomised trial (SUrveillance *vs* RadioFrequency ablation - SURF) is currently addressing this issue[61].

Based on the non-operative interventions which are successful in treating Barrett's oesophagus it has been suggested that population screening for this condition could decrease oesophageal cancer related mortality. Although previously the rate of conversion was frequently estimated at approximately 0.5% annually the true rate is likely to be less than this[62,63]. Two recently published large population based studies containing almost twenty thousand patients between them estimate the risk to be between 0.12%-0.38% per annum[64,65]. If rates of conversion of Barrett's oesophagus to oesophageal adenocarcinoma are indeed this low, stratification of patients into high and low risk patient groups for screening will be necessary in order to maximise benefits to screened patients while optimising resource utilization. American Gastroenterological Association Guidelines suggest screening for Barrett's neoplasia only in persons with multiple risk factors such as chronic reflux, hiatus hernia, age $\geqslant$ 50, male sex, white race, elevated body mass index, and intra-abdominal body fat distribution, and British Society of Gastroenterology guidelines broadly concur with these, recommending surveillance in persons with at least of the above three risk factors, and also in those with a first degree relative with Barrett's oesophagus or oesophageal adenocarcinoma[52,66]. The recommendation to screen first degree relatives is based on research demonstrating that familial clustering of Barrett's oesophagus is not uncommon, with up to 28% first degree relatives of patients with oesophageal junctional adenocarcinoma or Barrett's with high grade dysplasia also demonstrating a Barrett's mucosa[67,68]. Recent gene wide association studies have confirmed this genetic propensity with Barrett's associated loci demonstrated in the MHC and on Ch16q24[69]. With respect to risk stratification of patients for consideration of endoscopy, there is some evidence that the frequency of symptoms of gastroesophageal reflux influences the risk of oesophageal adenocarcinoma ($\geqslant$ once per week symptoms odds ratio 4.9 $\geqslant$ daily symptoms odds ratio 7.4), however, as up to 40% of patients with oesophageal cancer have no history of reflux, focusing solely on symptomatic patients will have limited benefits with respect to mortality[70,71]. As the potential morbidity of endoscopic surveillance not insignificant, novel non-invasive techniques for screening for Barrett's have been developed. These include a capsule sponge (Cytosponge) where the patients ingests a gelatin capsule containing a mesh which is attached to a string, which is then withdrawn through the oesophagus collecting cells which are identified as Barrett's using an immunohistochemical marker[72]. In a prospective cohort study of 504 patients who had undergone 3 mo or more acid suppression therapy in the previous five years compared to the gold standard of endoscopic surveillance, the sensitivity and sensitivity of the Cytosponge were 73% and 94% for 1 cm or more circumferential length Barrett's and 90% and 94% for clinically relevant segments of 2 cm or more. However, given the low incidence of Barrett's in the population studied (3%), clearly improved patient selection for screening is required.

CHEMOPREVENTION

The effects of aspirin therapy on the risk of cancer occurrence have been demonstrated in the multiple observational studies; use of aspirin is associated with a significantly decreased risk of cancer death in patients both with and without pre-existing malignancies[73,74]. The prostaglandin pathway is dysregulated in the development of oesophageal cancer, as increased expression of cyclooxygenase 2 (COX-2) has been demonstrated in Barrett's oesophagus and inhibition of COX-2 activity leads

to growth inhibition of oesophageal cancer cell lines *in vitro*[75,76]. Inhibition of COX-1 (and modification of COX-2 activity) using high dose (≥ 325 mg/d) aspirin appears to decrease the risk of developing Barrett's oesophagus in a case control study (OR = 0.36; $P = 0.001$), and a meta-analysis of multiple cohort studies confirms that aspirin (OR = 0.64, 95%CI: 0.52-0.79) or other NSAID (HR = 0.65, 95%CI: 0.50-0.85) use is associated with a lower risk of oesophageal adenocarcinoma[77,78]. The large UK ASPECT trial (NCT00357682) has recruited over 2500 patients with Barrett's oesophagus and randomised these to aspirin plus acid suppression therapy *vs* acid suppression therapy alone; the results of this study are eagerly awaited. A further large randomised worldwide study (Add-Aspirin) will begin recruitment in 2014 to assess whether aspirin given following surgical resection of oesophageal cancer will decrease the risk of recurrent disease. Although the epidemiological evidence for risk reduction due to aspirin is compelling, due to the lack of randomised data available, the potential toxicity associated with aspirin use, and potential biases of the current data, neither the American Gastroenterological Association nor the British Society of Gastroenterology recommend routine use of aspirin as a chemopreventative measure for decreasing the risk of Barrett's or oesophageal adenocarcinoma, although screening patients for cardiovascular risk factors for which aspirin therapy may be indicated is warranted[52,67].

CONCLUSION

Junctional adenocarcinoma is a challenging disease. The rate of its rapid increase in prevalence does not appear to have peaked, and if levels of obesity also continue to escalate worldwide it is likely to become a significant global health issue. Although precursor lesions exist which are amenable to curative therapy, identification of at risk patients who would benefit from screening is currently difficult. Once an invasive cancer is established it is clear that for most patients further therapy in addition to surgery will help improve survival. Whether this is peri-operative chemotherapy or neoadjuvant chemoradiotherapy is a matter of contention. This question has been difficult to answer in a straightforward manner due to the design of previous clinical trials, where patients with junctional adenocarcinoma have been treated alongside patients with squamous cell carcinoma of the proximal oesophagus or distal gastric cancers. For the purpose of clarity we believe that any future trials should not include squamous cell cancers, which have an entirely different disease biology, and if including distal gastric cancers are powered for a relevant subset analysis. Exploitation of the underlying molecular aberrations seen in oesophagogastric cancer, in particular amplification of receptor tyrosine kinases may lead to significant improvements in survival - however use of these agents is at this time predominantly limited to the metastatic setting. Increased uptake of PET directed therapy may allow superior selection of patients for intensified pre-operative regimens or immediate resection in the absence of response and this widely available biomarker is currently underutilised. Finally, it is hoped developments in the field of chemoprevention using the widely available and inexpensive medications such as aspirin may decrease the risk of progression of Barrett's oesophagus to overt malignancy at low cost and toxicity.

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