Predicting Response to Treatment in Gastroesophageal Junction Adenocarcinomas: Combining Clinical, Imaging, and Molecular Biomarkers

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Key Words. Gastroesophageal junction • Adenocarcinoma • Response • Positron emission tomography • Biomarkers

Disclosures

Gillian H. Bain: None; Russell D. Petty: None.

Section editors **Richard M. Goldberg** and **Patrick G. Johnston** have disclosed no financial relationships relevant to the content of this article.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias.

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Contrast the subtypes of gastroesophageal adenocarcinoma in order to select optimal therapeutic approaches for given subtypes.
2. Compare the various tools (CT, MRI, PET, PET-CT, etc.) for evaluating response to therapy in order to determine whether to initiate new therapy.
3. Evaluate response to neoadjuvant therapy, utilizing imaging, histopathology of resected specimens, and biomarkers, to plan postoperative treatment.

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ABSTRACT

The incidence of adenocarcinomas of the gastroesophageal junction (GEJ) is rapidly rising, and even in early-stage locoregional confined disease the 5-year survival rate rarely exceeds 25%–35%. Randomized trials and meta-analyses have demonstrated a benefit with neoadjuvant or perioperative chemotherapy and with neoadjuvant chemoradiotherapy. However, the optimal

approach in individual patients is not clear and remains controversial. A consistent finding is that patients who have a histopathological response to neoadjuvant therapy are more likely to receive a survival benefit. These clinical data provide a strong argument for the urgent development of methods to predict histopathological response to neoadjuvant therapies for GEJ adeno-

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carcinoma. Published data demonstrate that clinicopathological features (tumor location), imaging (fluorodeoxyglucose-positron emission tomography “metabolic response”), and tissue/molecular biomarkers may all have a predictive value for neoadjuvant therapies. However, it is uncertain from published data whether or not they will be useful for clinical decision making in individual patients. Existing candidate biomarkers need to be properly qualified and validated

and novel biomarkers are required; and an optimal approach should involve the combination and integration of clinical, imaging, and molecular biomarkers. This review presents the evidence base and discusses novel experimental approaches for the combination of biomarker modalities to allow optimization of an individualized treatment approach in GEJ adenocarcinoma patients that may be relevant to other tumor types as well. *The Oncologist* 2010;15:270–284

INTRODUCTION

The clinical management of early operable adenocarcinomas of the gastroesophageal junction (GEJ) provides a clear paradigm for the application of predictive biomarkers [1]. International consensus is that chemotherapy and/or radiotherapy in addition to surgery improves outcome; however, there is disagreement regarding the optimal approach. Randomized clinical trial data support the use of either preoperative (neoadjuvant) chemotherapy, perioperative (neoadjuvant and adjuvant) chemotherapy, or preoperative concurrent chemoradiotherapy [2–7]. Accordingly, a central translational research objective for GEJ adenocarcinomas is to define subgroups of patients who optimally benefit from particular combined-modality approaches [1]. Unfortunately, interpretation of clinical trials is complicated by heterogeneity in trial data, both with regard to patient populations—for example, a mix of histology in older studies (squamous and adenocarcinoma), a mix of tumor types (esophageal, GEJ, and gastric), and different staging protocols (multidetector [or not] computed tomography [CT], endoscopic ultrasound [EUS], laparoscopy, endobronchial ultrasound, fluorodeoxyglucose-positron emission tomography [FDG-PET], or FDG-PET/CT)—and also with regard to all aspects of treatment protocols (surgery, chemotherapy, and radiotherapy). New approaches to clinical investigation to identify predictive biomarkers are needed and discussed in this review.

CLINICAL EPIDEMIOLOGY OF GASTROESOPHAGEAL ADENOCARCINOMAS AND DISEASE SUBTYPES

Gastroesophageal carcinomas have undergone distinct changes in their epidemiology over recent years [8]. The incidence of gastric adenocarcinoma is declining, but in western countries (but not Asian countries) there is an ongoing rise in adenocarcinomas of the distal esophagus and GEJ of more than sixfold in the past three decades [9]. This rising incidence has led to the recognition of adenocarcinoma of the GEJ as a distinct disease entity and the need to reclassify esophageal and gastric adenocarcinomas to reflect this [10]. Data support a classification with disease subtypes with differences in etiology, pathogenesis, and natural history (Ta-

ble 1). According to U.S. cancer registry statistics, the 5-year survival rate is only 10%–15% overall, and in early-stage, locoregional, confined disease the 5-year survival rate is 25%–30% [11].

This review is concerned with the emerging predominant group, adenocarcinomas of the GEJ, defined as tumors occurring within 5 cm proximal or distal to the GEJ [10]. The recognition of subtypes of gastroesophageal adenocarcinomas is important for locoregional management [3, 12]. Although it is of less relevance for systemic treatment with cytotoxic drugs [13], emerging data with targeted therapy suggest differential responses for these clinicopathological subtypes (Table 1) with novel targeted agents (e.g., the epidermal growth factor receptor [EGFR] tyrosine kinase inhibitor erlotinib [14]), and this is supported by data showing differential expression of targets and biomarkers in these disease subgroups (e.g., human epidermal growth factor receptor [HER]-2) [15]. Recognition of these known disease subgroups is important for predictive biomarker investigation, especially discovery, particularly if a differential benefit of the intervention is seen in different subgroups. Here, unless disease subgroups are acknowledged, the biomarker discovered or being investigated may ultimately prove to be a surrogate for disease subtype rather than clinical benefit or response and therefore of no clinical utility as a predictive biomarker.

RESPONSE ASSESSMENT TO NEOADJUVANT THERAPY IN EARLY GEJ ADENOCARCINOMAS AS A SURROGATE FOR CLINICAL EFFICACY

There has been considerable interest in response to neoadjuvant therapy as a surrogate for survival benefit both in terms of the therapy modality being used and also as a prognostic factor for outcome following surgery [1]. A number of methods of response assessment have been evaluated in GEJ adenocarcinomas as surrogates for survival.

Clinical Response

Clinical response to therapy is often inconsistently defined, varies according to study, and correlates poorly with survival [1].

Table 1. Classification of gastroesophageal cancers based upon differences in etiology, pathogenesis, and natural history

Disease group	Subgroup	Etiology	Natural history	Response to therapy
Esophageal	Squamous cell carcinoma	Smoking, alcohol consumption; incidence declining in western countries [77]	Early regional lymph node dissemination; distant relapse less likely than with adenocarcinoma [78–80]	Survival comparable with nonsurgical treatment with concurrent chemoradiotherapy and surgical resection [81–83]
	Adenocarcinoma	Male gender, obesity, GERD/esophagitis, Barrett's esophagus, and intestinal metaplasia [3]	Distant relapse more likely than with squamous cell carcinoma [78–80]	Greater benefit from neoadjuvant chemotherapy than in squamous cell carcinomas [84]
GEJ (center of tumor located within 5 cm proximal or distal to GEJ)	Type I (center or two thirds of tumor >2 cm proximal to GEJ)	Male gender, obesity, GERD/esophagitis, Barrett's esophagus, and intestinal metaplasia [10]	Can metastasize both to mediastinal nodes and to abdominal nodes; natural history as distal esophageal adenocarcinoma; lymphatic vessel invasion less common than with types II and III and not independently prognostic [85]	Surgical resection and treatment approaches similar to those for distal esophageal adenocarcinomas applicable [10]
	Type II (center or two thirds of tumor located <2 cm proximal and <1 cm distal to GEJ)	Male gender, but less strong than with type I; only 10% associated with GERD/esophagitis, Barrett's esophagus, and intestinal metaplasia [10]	More commonly metastasize to abdominal nodes. Lymphatic vessel invasion more common than with type I and is independently prognostic [85]	Surgical resection and treatment approaches similar to those for gastric adenocarcinomas applicable, although this is controversial [10]
	Type III (center or two thirds of tumor >1 cm distal to GEJ)	Not associated with GERD/esophagitis, Barrett's esophagus, and intestinal metaplasia [10]	Metastasize to abdominal nodes, rare to metastasize to mediastinal nodes; natural history as with gastric carcinomas; lymphatic vessel invasion more common than with type I and is independently prognostic [85]	Surgical resection and treatment approaches similar to gastric adenocarcinomas applicable [10]
Gastric	Distal	<i>Helicobacter pylori</i> , atrophic gastritis, smoking; most prevalent type in developing world, declining in western countries [86]	Metastasize to abdominal nodes, rare to metastasize to mediastinal nodes; transcelomic spread in peritoneal cavity can occur [87]	Locoregional recurrence rates after surgery high—may be role for more extensive lymphadenectomy and adjuvant chemoradiotherapy, although this is controversial [88]

Abbreviations: GEJ, gastroesophageal junction; GERD, gastroesophageal reflux disease.

Radiological Response

Radiological response assessed by CT, and as defined by the Response Evaluation Criteria in Solid Tumors, is often used in current routine clinical practice and clinical trials [16]. However, a decline in tumor size is a relatively late event in response to chemotherapy or radiotherapy, limiting its use as a predictive biomarker. In addition, the presence of fibrotic or

necrotic tissue may not accurately reflect the viable tumor cell fraction in a residual mass. Thus, esophageal thickness and tumor response measured by CT does not correlate with survival, meaning that it is not a useful surrogate for survival and has limited clinical utility for assessing benefit from neoadjuvant therapy and as a prognostic factor to facilitate subsequent clinical treatment decisions [1, 17].

Metabolic Response

Several workers have evaluated the potential of serial FDG-PET scans during the course of neoadjuvant therapy to define a metabolic response or nonresponse and to use this as a predictive biomarker or surrogate for benefit from neoadjuvant therapy and allow therapy to be changed early if it is likely to be ineffective [18–27]. These studies are discussed in detail below; however, in summary, preliminary evidence supports a role for FDG-PET–defined metabolic response as a potentially useful surrogate for survival benefit from neoadjuvant chemotherapy in particular [21, 23–26]. Confirmatory retrospective and prospective studies are needed, and the greater value of metabolic response may be to predict histopathological response, which has been shown to be a stronger surrogate for survival benefit following neoadjuvant therapy than is metabolic response [26].

Histopathological Response

Histopathological response to treatment appears to have value as a surrogate for survival in GEJ adenocarcinomas. A consistent finding is that histopathological response identifies patients who benefit from both neoadjuvant chemotherapy and chemoradiotherapy, and patients who do not respond to neoadjuvant therapy have survival rates that may not be significantly different from those who are treated with surgery alone [1, 5, 28–30]. Therefore, the ability to predict histopathological response to neoadjuvant therapy would allow optimal combined-modality treatment selection preoperatively. In addition, the subsequent confirmation (or otherwise) of histopathological response may facilitate subsequent postoperative (adjuvant) therapy (Fig. 1). Implicit in this statement is the hypothesis that histopathological response is indicative of the underlying disease biology, although the molecular mechanisms behind this are not known.

DEFINITION OF HISTOPATHOLOGICAL RESPONSE

Histopathological response has been defined by a variety of methods commonly involving estimation of the percentage of viable tumor relative to therapy-induced fibrosis [30–34]. The validated Becker [31] and Mandard [32] scoring systems are used in gastroesophageal cancer (Table 2). A major histopathological response is often defined as “<10% residual tumor cells” (Mandard grade 1 and grade 2, Becker grade 1a and grade 1b). Histopathological response evaluation requires resection of the tumor and can be determined only at the end of treatment, and cannot be used to modify preoperative treatment. Ideally, other measures of response that can predict histopathological response are needed.

In the remainder of this review we discuss the potential use of biomarkers to predict histopathological response to preoperative therapies in GEJ adenocarcinoma. It is envis-

Figure 1. Predictive biomarkers in gastroesophageal junction adenocarcinomas. A biomarker predictive of histopathological response, and hence survival benefit from a neoadjuvant therapy, may also be predictive for adjuvant use of the same therapy and may also have therapy-independent prognostic value. Histopathological response has prognostic value and may confirm or modify the relevance of a predictive biomarker, and hence influence adjuvant therapy decisions.

Table 2. Mandard and Becker scoring systems for histopathological response in gastroesophageal cancer

Grade Description

Mandard regression grade [32]

1	Absence of residual cancer, fibrosis extending through different areas of esophageal wall
2	Rare residual cancer cells scattered through fibrosis
3	Increase in number of residual cancer cells but fibrosis still predominant
4	Residual cancer outgrowing fibrosis
5	Absence of regressive changes

Becker regression grade [31]

1a	No residual tumor/tumor bed
1b	<10% residual tumor/tumor bed
2	10%–50% residual tumor/tumor bed
3	>50% residual tumor/tumor bed

aged that the clinical use of such predictive biomarkers will provide the means to stratify patients for combined-modality therapy in a clinical management paradigm similar to that outlined in Figure 2.

CLINICOPATHOLOGICAL PREDICTIVE BIOMARKERS

Anatomical Disease Classification

The classification of GEJ adenocarcinomas outlined in Table 1 reveals etiological and histological differences and

Figure 2. Paradigm for the use of predictive biomarkers to stratify preoperative therapy selection in gastroesophageal junction (GEJ) adenocarcinomas. Histopathological response can be subsequently used for confirmation or modification of adjuvant therapy. This requires prospective qualification and validation of predictive biomarkers before implementation. Randomization between alternative treatments is also possible in this paradigm.

represents a practical and pragmatic disease classification based upon the anatomical location of the tumor, which can be applied in clinical practice with the use of routine staging procedures preoperatively (endoscopy, EUS, CT, laparoscopy) and postoperatively (histopathology). Distinct patterns of lymph node spread have been defined for type I, type II, and type III GEJ adenocarcinomas, and proposals for optimized treatment volumes for preoperative and definitive chemoradiotherapy have been made using this [12]. Distinct pathogenesis and biological features are implied by the observations of distinct etiologies and histological features, and recent and current therapeutic trials have recognized this by the definition of inclusion criteria based upon this disease classification [6, 35]. These clinical trials will provide data for hypothesis generation regarding the biological basis and therapeutic relevance of anatomical GEJ adenocarcinoma classification, which at present are not defined. It is important for the use of biomarker protocols to recognize these disease subtypes, because clinical response phenotypes may be different in each, and accordingly biomarkers must be able to delineate between being predictive for clinical benefit and being diagnostic or surrogates/markers for disease subtype. This is well illustrated by early clinical trial data of the oral tyrosine kinase inhibitor erlotinib, whereby differential sensitivity between GEJ adenocarcinomas and gastric adenocarcinomas was demonstrated [14].

Clinical Symptoms

Measurable clinical symptoms such as dysphagia (dysphagia scores) and weight gain have been evaluated as predictive biomarkers. However, although improvements in

dysphagia or weight gain following neoadjuvant chemotherapy correlate with radiological response, they do not correlate with histopathological response [36].

Rebiopsy of Tumors

Endoscopic rebiopsy of tumors after completion of neoadjuvant therapy has been evaluated as a means to predict histopathological response, but this approach is unreliable in the prediction of response [31, 37].

IMAGING PREDICTIVE BIOMARKERS

Anatomical Imaging

Endoscopy

Macroscopic appearance after treatment is associated with histopathological response, but with a limited accuracy of 50% (sensitivity, 57%; specificity, 36%) [37].

CT and EUS

CT scans are routinely performed following the completion of neoadjuvant therapy. However, they are of limited sensitivity and specificity in histopathological response assessment [38]. Progressive disease on CT after therapy is a well-acknowledged surrogate for the absence of clinical benefit from therapy in malignancy in general [16]. In early GEJ adenocarcinomas, CT progression identifies primary chemotherapy- or chemoradiotherapy-resistant disease associated with a very poor prognosis and provides a strong argument for avoidance of surgery in such patients. In a systematic review on assessment of histopathological response to therapy using CT, EUS, and FDG-PET, EUS was superior to CT, with sensitivities of 50%–100% and specificities

Table 3. Studies evaluating the potential of FDG-PET to predict histopathological response/survival of GEJ adenocarcinoma to neoadjuvant treatment

Study	Sample size	Tumor type	Tumor site	Measurement of tracer uptake	Neoadjuvant treatment	Timing of PET	Histopathological response score	Definition of PET response	Outcome
Weber et al. (2001) [23]	40	A	Type I and type II GEJ	SUV	Chemotherapy	Pretreatment, day 14 of treatment	Mandard	R, >35% reduction in SUV; NR, ≤35% reduction in SUV	2-Yr survival: R, 60%; NR, 37% ($p = .04$)
Flamen et al. (2002) [18]	36	A/SCC	Esophagus or GEJ	TLR	CRT	Pretreatment, post-treatment	Other	R, >80% reduction in TLR; NR, ≤80% reduction in TLR	Median survival: R, 16.3 mos; NR, 6.4 mos ($p = .01$)
Downey et al. (2003) [22]	39	A/SCC	Distal two thirds of esophagus	SUV	CRT	Pretreatment, post-treatment	Not defined	R, >60% reduction in SUV; NR, ≤60% reduction in SUV	2-Yr survival: R, 89%; NR, 64% ($p = .08$); DFS: R, 67%; NR, 38% ($p = .05$)
Kroep et al. (2003) [24]	13	A/SCC	Esophagus or GEJ	SUV/Kinetic analysis	Chemotherapy	Pretreatment, after 2 cycles, post-treatment	Mandard	R, >40% reduction in SUV; NR, ≤40% reduction in SUV (from pretreatment to after 2 cycles). R, >60% reduction in SUV; NR, ≤60% reduction in SUV (from pre- to post-treatment)	PET performed post-treatment had better accuracy for predicting pathological response than PET performed during therapy (sensitivity and specificity, 100% and 100% versus 100% and 86%)
Brink et al. (2004) [20]	20	A/SCC	Esophagus	SUV	CRT	Pretreatment, post-treatment	Mandard	Not defined	No correlation between change in SUV and Mandard tumor regression grade
Swisher et al. (2004) [19]	83	A/SCC	Esophagus or GEJ	SUV	CRT	Pretreatment, post-treatment	Other	Not defined	Post-therapy SUV correlated with pathology ($p = .01$); post-therapy SUV ≥ 4 associated with shorter survival ($p = .01$)
van Westreenen et al. (2005) [43]	40	A/SCC	Esophagus or GEJ	SUV	None	Pretreatment	Survival	Not defined	SUV >6.7 correlated with shorter survival ($p = .016$)
Gillham et al. (2006) [27]	32	A/SCC	Esophagus or GEJ	SUV	CRT	Pretreatment, day 7 of treatment	Mandard	Not defined	No correlation between change in SUV and Mandard tumor regression grade
Ott et al. (2006) [25]	65	A	Type I and type II GEJ	SUV	Chemotherapy	Pretreatment, day 14 of treatment	Becker	R, >35% reduction in SUV; NR, ≤35% reduction in SUV	3-Yr survival: R, 70%; NR, 35% ($p = .01$)

continued

Table 3. (Continued)

Study	Sample size	Tumor type	Tumor site	Measurement of tracer uptake	Neoadjuvant treatment	Timing of PET	Histopathological response score	Definition of PET response	Outcome
Wieder et al. (2007) [21]	24	A	Type I and type II GEJ	SUV	Chemotherapy	Pretreatment, day 14 of treatment, post-treatment	Becker	R, >35% reduction in SUV; NR, ≤35% reduction in SUV (from pretreatment to day 14). R, ≥63% reduction in SUV; NR, <63% reduction in SUV (from pre- to post-treatment)	3-Yr survival: R, 83%; NR, 33% ($p = .03$) (from pretherapy to day 14). 3-Yr survival: R, 73%; NR, 46% ($p = .09$) (from pre- to post-treatment)
Lordick et al. (2007) [26]	110	A	Type I and type II GEJ	SUV	Chemotherapy	Pretreatment, day 14 of treatment	Becker	R, ≥35% reduction in SUV; NR, <35% reduction in SUV	Median survival: R, not reached; NR, 25.8 mos ($p = .015$)

Abbreviations: A, adenocarcinoma; CRT, chemoradiotherapy; DFS, disease-free survival; FDG-PET, fluorodeoxyglucose-positron emission tomography; GEJ, gastroesophageal junction; NR, metabolic nonresponder; R, metabolic responder; SCC, squamous cell carcinoma; SUV, standardized uptake value; TLR, tumor to liver ratio.

of 36%–100%, compared with 33%–55% and 50%–71%, respectively, for CT [39]. However, EUS is an invasive procedure, and in 20%–50% of cases the probe cannot be passed through the narrowed esophagus. Moreover, the EUS technique is not as widespread as CT scanning, mainly because of the limited availability of operators with sufficient expertise. In addition, the need to ensure the lack of distant progression at least by CT is considered mandatory by all clinicians before radical treatment such as surgical resection is planned.

Functional Imaging

Biochemical and molecular imaging potentially offer significant advantages in evaluating histopathological response over anatomical imaging by detecting changes, for example, the decrease in cell proliferation, increase in cell death, and decline in the number of viable tumor cells that precede a decline in tumor size [40].

PET

PET allows noninvasive visualization and quantitative assessment of physiological and biochemical processes within tumors [41]. [^{18}F]-2-fluoro-2-deoxy-d-glucose (^{18}F FDG) is the glucose analog 2-deoxy-d-glucose labeled with ^{18}F and is by far the most commonly used radiopharmaceutical for oncological PET studies. The use of ^{18}F FDG is based on differences in aerobic glycolysis between nonmalignant and malignant cells, although the molecular mechanisms that determine greater ^{18}F FDG uptake in tumors are inadequately understood [42]. Several studies have evaluated the potential of FDG-PET to predict histopathological response/survival with neoadjuvant treatment in GEJ cancers (Table 3).

Pretreatment FDG-PET

Conflicting results have been reported in the use of pretreatment FDG-PET to predict histopathological response [18–27, 43]. Several authors have demonstrated that the predictive value of changes in tumor ^{18}F FDG uptake with serial imaging during therapy is superior to measurements of absolute pretherapy ^{18}F FDG uptake (Table 3).

Serial FDG-PET

A number of studies have demonstrated the ability of serial FDG-PET imaging early in the course of neoadjuvant treatment to predict histopathological response (Table 3) [21, 23–26]. There are significant issues yet to be resolved with regard to the standardization of PET imaging protocols [44], and the optimal method and time point for repeat imaging is not fully resolved. Ideally, this would be as soon as possible after the start of treatment, thereby allowing potentially toxic therapy to be discontinued in those identified as nonresponders. Most studies performing FDG-PET imag-

ing during therapy have performed them on day 14 of treatment [21, 23, 25, 26]. In contrast, Gillham et al. [27] performed them on day 7 of treatment. The optimal time point is likely to be different for chemotherapy than for chemoradiotherapy, and may be different again for novel targeted therapies. This most likely reflects the different therapeutic mechanisms of these different treatment modalities, for example, the acute and chronic inflammatory response to radiation and the contribution of host stromal reaction to therapy [45].

The strongest data supporting the use of FDG-PET as a predictive biomarker are derived from prospective studies in GEJ adenocarcinomas [21, 23, 25, 26]. The data are unicentric from a specialized, high-volume center performed using a PET, not PET-CT, scanner and clearly need multicentric evaluation. Initially, Weber et al. [23] demonstrated, in a prospective study of patients with locally advanced GEJ adenocarcinomas, that a reduction in metabolic activity after 2 weeks of chemotherapy was correlated with a subsequent decrease in tumor size, a higher rate of curative resections ($p = .01$), histopathological tumor regression ($p = .001$), and patient survival ($p = .04$). These prospectively collected data allowed the authors to define an optimal cutoff value of a 35% reduction in standard uptake value (SUV) (day 14 from baseline) to distinguish responding and nonresponding tumors with a sensitivity of 93% (95% confidence interval [CI], 68%–100%) and specificity of 95% (95% CI, 77%–100%) [23]. This definition was then validated prospectively in a larger population with longer follow-up. Metabolic responders (i.e., those with a reduction in ^{18}F FDG uptake of 35% 14 days after the initiation of therapy) showed a histopathological response rate of 44%, with a 3-year survival rate of 70%. In contrast, prognosis was poor for metabolic nonresponders, with a histopathological response rate of 5% ($p = .001$) and a 3-year survival rate of 35% ($p = .01$). A multivariate analysis demonstrated that metabolic response was the only factor that predicted recurrence ($p = .018$) in patients whose tumors were completely resected [25]. Early metabolic response (14 days after the start of therapy) provided at least the same accuracy for prediction of treatment outcome as with late ^{18}F FDG changes (3 months after the start of therapy) [21], and FDG-PET after completion of chemotherapy did not result in a higher accuracy for the prediction of histopathological response.

Subsequently, the Metabolic response evaluation for Individualisation of neoadjuvant Chemotherapy in esophageal and esophagogastric adenocarcinoma trial assessed the feasibility of a PET response-guided treatment algorithm. FDG-PET scans were performed at baseline and 14 days after the start of chemotherapy (i.e., after one cycle).

Patients whose tumor SUV had decreased by $\geq 35\%$ were defined as metabolic responders and went on to receive further chemotherapy before undergoing surgery. Metabolic nonresponders discontinued chemotherapy and proceeded to surgery. Metabolic responders were found to have a good long-term prognosis, with a median overall survival duration not yet reached, whereas nonresponders had a median overall survival time of 25.8 months (hazard ratio [HR] 2.13; 95% CI, 1.14–3.99; $p = .015$) [26]. Together with previous investigations, that study suggested that FDG-PET may provide an effective predictive biomarker to identify nonresponders to neoadjuvant chemotherapy, with a major histopathological response rate of $<5\%$ in FDG-PET early metabolic nonresponders, and a definitive randomized trial is needed and planned to determine clinical utility [25, 26]. However, whereas FDG-PET early metabolic responders had a higher histopathological response rate, approximately 50% of those predicted to have a response did not, and therefore do not receive clinical benefit from neoadjuvant therapy. This problem is clearly illustrated by the HR of 4.55 (95% CI, 1.37–15.04; $p = .004$) for survival between those who have an FDG-PET metabolic response and a major histopathological response and those who have an FDG-PET early metabolic response but no histopathological response [26]. Therefore, histopathological response after neoadjuvant chemotherapy remains the strongest indicator of long-term clinical outcome, and so has value as a prognostic indicator (assessed after therapy) but no predictive value to assist in planning of optimized neoadjuvant therapy (Fig. 1).

Accordingly, improvement in the accuracy of early prediction of response remains a key aim for research. A better understanding of the biological basis of FDG-PET metabolic response and subsequent histopathological response or nonresponse would be valuable and also provide insights into tumor biology that would be of therapeutic relevance. Although a change in ^{18}F FDG uptake has been demonstrated to be indicative of a lower viable cell number and lower rate of glucose metabolism per cell [45], the molecular pathways and mechanisms of a decrease in ^{18}F FDG uptake following cytotoxic chemotherapy are unknown and may be treatment and tumor type specific [46]. Caution is necessary in making unvalidated generalizations. In particular, studies based on examination of specific pathways and approaches have so far failed to provide a molecular basis for the greater uptake of ^{18}F FDG in tumors and the decrease that characterizes early metabolic response to therapy.

MOLECULAR PREDICTIVE BIOMARKERS

Table 4 summarizes the studies that have demonstrated the predictive value of a number of molecular biomarkers in as-

Table 4. Studies demonstrating the potential of molecular markers to predict histopathological response/survival of patients with GEJ adenocarcinoma given neoadjuvant treatment

Type of cellular pathway/factor	Marker/type of change	Timing of measurement	Sample size	Tumor type	Tumor site	Neoadjuvant treatment	Methods	Histopathological response score	Outcome	Study
Transcription factors	NF- κ B –ve	Pretreatment	58	A	Esophagus	CRT	Electrophoretic mobility shift assay, western blot, IHC	Other	PathR $\uparrow$ ($p = .0001$); survival $\uparrow$ ($p < .05$)	Abdel-Latif et al. (2004) [47]
Growth factor receptors	NF- κ B +ve	Pretreatment	37	A/SCC	Esophagus and GEJ	CRT	IHC	Other	PathR $\downarrow$ ($p = .05$); OS $\downarrow$ ($p = .06$)	Izzo et al. (2006) [48]
	NF- κ B +ve	Pretreatment	75	A/SCC	Esophagus and GEJ	CRT	IHC	Other	PathR $\downarrow$ ($p = .006$); disease-free survival $\downarrow$ ($p = .007$); OS $\downarrow$ ($p = .009$)	Izzo et al. (2006) [49]
	EGFR $\downarrow$	Pretreatment	54	A/SCC	Esophagus and GEJ	CRT	IHC	Other	OS $\uparrow$ ($p = .009$)	Gibson et al. (2003) [50]
Angiogenic factors	EGFR $\downarrow$	Pretreatment to resection	22	A/SCC	Esophagus	CRT	PCR	Junker	PathR $\uparrow$ ($p = .014$)	Schneider et al. (2005) [51]
	HER-2 $\downarrow$	Pretreatment	36	A/SCC	Esophagus	CRT	PCR	Junker	PathR $\uparrow$ ($p = .015$)	Miyazono et al. (2004) [52]
	Vascular endothelial growth factor $\downarrow$	Pretreatment	56	A/SCC	Esophagus	CRT	IHC	Other	PathR $\uparrow$ ($p = .035$); survival $\uparrow$ ($p = .021$)	Imdahl et al. (2002) [53]
Tumour suppressor genes	<i>p53</i> mutation	Pretreatment	46	A/SCC	Esophagus and GEJ	CRT	PCR, DNA sequencing	Other	OS $\uparrow$ ($p = .051$)	Gibson et al. (2003) [50]
	<i>p53</i> +ve	Pretreatment	48	A/SCC	Esophagus and GEJ	CRT/Chemotherapy	IHC	Other	PathR $\downarrow$ ($p = .024$)	Beardmore et al. (2003) [54]
	<i>p53</i> +ve to –ve	Pretreatment to resection	23	A	Esophagus and GEJ	Chemotherapy	IHC	Other	PathR $\uparrow$ ($p = .003$); OS $\uparrow$ ($p = .036$)	Heeren et al. (2004) [55]
Cell cycle regulators	p21 –ve to +ve	Pretreatment to resection	23	A	Esophagus and GEJ	Chemotherapy	IHC	Other	PathR $\uparrow$ ($p = .003$); OS $\uparrow$ ($p = .036$)	Heeren et al. (2004) [55]
Nucleotide excision repair pathway	<i>ERCC1</i> $\downarrow$	Pretreatment	36	A/SCC	Esophagus	CRT	PCR	Junker	PathR $\uparrow$ ($p < .001$)	Wamecke-Eberz et al. (2004) [56]
	<i>ERCC1</i> $\uparrow$	Pretreatment	84	A/SCC	Esophagus	CRT	PCR	Other	Survival $\downarrow$ ($p = .071$)	Joshi et al. (2005) [57]
	Survivin $\uparrow$	Pretreatment	51	A/SCC	Esophagus	CRT	PCR	Junker	PathR $\leftrightarrow$, OS $\uparrow$ ($p < .003$)	Wamecke-Eberz et al. (2005) [58]
Apoptotic factors	TS $\uparrow$	Pretreatment	69	A/SCC	Esophagus	CRT	PCR	Other	PathR $\downarrow$ ($p < .001$); survival $\downarrow$ ($p = .007$)	Joshi et al. (2005) [57]
	TS +ve	Pretreatment	118	A/SCC	Esophagus	CRT	IHC	Other	Survival $\downarrow$ ($p = .04$)	Harpole et al. (2001) [59]
	TS $\downarrow$	Pretreatment to resection	21	A	Esophagus	Chemotherapy	PCR	Becker	PathR $\uparrow$ ($p = .028$)	Langer et al. (2007) [60]
	Thymidine phosphorylase $\downarrow$	Pretreatment	21	A	Esophagus	Chemotherapy	PCR	Becker	PathR $\uparrow$ ($p = .013$)	Langer et al. (2007) [60]
	Dihydropyrimidine dehydrogenase $\downarrow$	Pretreatment	21	A	Esophagus	Chemotherapy	PCR	Becker	PathR $\uparrow$ ($p = .032$)	Langer et al. (2007) [60]

continued

Table 4. (Continued)

Type of cellular pathway/factor	Marker/type of change	Timing of measurement	Sample size	Tumor type	Tumor site	Neoadjuvant treatment	Methods	Histopathological response score	Outcome	Study
	Methylene-tetrahydrofolate reductase ↑	Pretreatment	38	A	Esophagus	Chemotherapy	PCR	Becker	PathR ↑ ($p = .012$); survival ↑ ($p = .015$)	Langer et al. (2005) [61]
	MRP1 ↑	Pretreatment	38	A	Esophagus	Chemotherapy	PCR	Becker	PathR ↑ ($p = .007$); survival ↑ ($p = .017$)	Langer et al. (2005) [61]
	MRP1 ↓	Pretreatment to resection	21	A	Esophagus	Chemotherapy	PCR	Becker	PathR ↑ ($p = .018$) (pretherapy); PathR ↑ ($p = .041$) (pretherapy to resection)	Langer et al. (2007) [60]
	GST- π + ve	Pretreatment	118	A/SCC	Esophagus	CRT	IHC	Other	Survival ↓ ($p = .02$)	Harpole et al. (2001) [59]
	GST- π ↓	Pretreatment	93	A/SCC	Esophagus	CRT	PCR	Other	Survival ↓ ($p = .05$)	Joshi et al. (2005) [57]

Abbreviations: A, adenocarcinoma; CRT, chemoradiotherapy; EGFR, epidermal growth factor receptor; *ERCC1*, excision crosscomplementing gene 1; GEJ, gastroesophageal junction; GST- π , glutathione S-transferase- π ; HER, human epidermal growth factor receptor; IHC, immunohistochemistry; MRP1, multidrug resistance protein 1; NF- κ B, nuclear factor κ B; OS, overall survival; PathR, histopathological response; PCR, polymerase chain reaction; SCC, squamous cell carcinoma; TS, thymidylate synthase.

sessing histopathological response/survival in GEJ cancer patients with neoadjuvant therapy [47–61]. None of the biomarkers available have been prospectively tested, and most studies are on small patient populations. Those molecular biomarkers that are likely to be relevant to future targeted therapies or have shown consistently positive results for histopathological response prediction are discussed below.

Nuclear Factor- κ B

Nuclear factor- κ B appears to hold promise as a predictive biomarker following neoadjuvant chemoradiotherapy [47–49, 62].

EGFR Family

Expression of EGFR is found in 29%–92% of patients with esophageal cancer [63]. Amplification of *HER-2* has been seen in 15%–19% of esophageal adenocarcinomas [15, 64]. Although results for EGFR and histopathological response/survival prediction with chemoradiotherapy have generally been positive [50, 51], the method of assay of EGFR (immunohistochemistry [IHC], mutation) may determine the predictive impact, and optimal methods of assessment in this predictive context are yet to be resolved. The same applies to the use of novel EGFR-targeted agents, and both monoclonal antibodies and small molecules are in early-phase clinical trials in the neoadjuvant setting [65, 66]. Although limited, data so far suggest that *EGFR* mutation appears to be relatively infrequent in GEJ adenocarcinomas, and therefore clinically effective translation of *EGFR* mutation as a predictive biomarker for EGFR-targeted agents, as has been proven to be useful in non-small cell lung cancer (NSCLC) patients, seems unlikely. Similarly, although *K-ras* has clinical utility as a predictive biomarker for EGFR-targeted agents in colorectal adenocarcinomas and NSCLC, *K-ras* is wild type in 70%–80% of gastroesophageal cancer patients (much higher than in NSCLC and colorectal cancer patients), so its impact and use as a biomarker may be limited in gastroesophageal cancer.

Updated results of a preplanned subgroup analysis of the Trastuzumab in Gastric Cancer (ToGA) trial (a phase III randomized trial of cisplatin and 5-fluorouracil or capecitabine with or without trastuzumab in advanced gastric and GEJ adenocarcinomas) have suggested that HER-2 IHC (score 3+) with the use of HER-2 fluorescence in situ hybridization in borderline IHC (score 2+) cases predicts those patients who will benefit from the addition of trastuzumab [15], and these data are potentially transferable to predictive biomarker use in the neoadjuvant setting. Trastuzumab is being assessed in the neoadjuvant setting; however, results may have to be readdressed in light of the HER-2 predictive biomarker data from the ToGA trial [15].

Vascular Endothelial Growth Factor

A potential predictive role for vascular endothelial growth factor (VEGF) was reported by Imdahl et al. [53], who found that, for patients undergoing neoadjuvant chemoradiotherapy, a higher VEGF index in pretreatment biopsies correlated with a poorer histopathological response ($p = .035$) [53]. Several early-phase trials are investigating anti-VEGF or anti-VEGF receptor agents in GEJ patients in the advanced setting [67–70], and the U.K. STO3 phase II/III trial is evaluating standard neoadjuvant chemotherapy with or without bevacizumab in patients with gastric and type III GEJ adenocarcinomas.

Gene Expression Profiling

Luthra et al. [71] performed oligonucleotide microarrays on pretreatment endoscopic biopsies from 19 patients (16 with adenocarcinoma, two with squamous cell carcinoma, and one with adenosquamous carcinoma) prior to neoadjuvant chemoradiotherapy. Unsupervised hierarchical cluster analysis segregated the cancers into two molecular subtypes, consisting of 10 and nine specimens, respectively. Most cancers (five of six) that had a complete pathological response clustered in molecular subtype I. Subtype II, with one exception, consisted of cancers with less than a complete pathological response. Levels of p53 effector related to peripheral myelin protein 22, S100A2 (which encodes a calcium binding protein), and SPRR3 (a small proline-rich protein) allowed discrimination of complete from less than complete pathological response with high sensitivity and specificity (85%). Pathway analysis identified the apoptotic pathway as one of the key functions downregulated in molecular subtype II, in comparison with molecular subtype I [71].

Using cDNA microarrays to compare gene expression profiles, Greenawalt et al. [72] identified 3,516 genes that were differentially expressed among normal esophageal tissue, esophageal adenocarcinoma, squamous cell carcinoma, and Barrett's esophagus, and allowed separation in unsupervised hierarchical cluster analysis consistent with histology. These data may be useful to identify the molecular mechanisms underlying the different behavior and responsiveness to treatment of these histological disease subtypes [72].

DISCUSSION

MECHANISMS AND PARADIGMS FOR STRATIFIED CLINICAL DECISION MAKING IN EARLY GEJ ADENOCARCINOMAS

A key translational research objective for GEJ adenocarcinomas is to define subgroups of patients with optimal survival from particular combined-modality treatment approaches. Clinical and radiological responses are not re-

liable as surrogates for survival. However, a consistent finding is that histopathological response identifies patients with longer survival times both after neoadjuvant chemotherapy and after chemoradiotherapy [5, 28, 29]. Histopathological response can only be determined at the time of resection and so the ability to predict histopathological response earlier in the course of neoadjuvant therapy would be beneficial. Prediction of histopathological response to neoadjuvant therapy would allow optimal combined-modality treatment selection, and the subsequent determination of histopathological response or nonresponse may facilitate subsequent clinical treatment decisions for post-operative (adjuvant) therapy. This provides a useful model for clinical investigation and a paradigm for stratified clinical decision making in early gastroesophageal adenocarcinoma that is potentially readily transferable to clinical practice (Figs. 1 and 2).

Current data do not provide definitive answers regarding the optimal methods to predict histopathological response. Recent guidance on biomarker development is useful and should be applied to subsequent investigations with predictive biomarkers in GEJ adenocarcinomas for both existing candidate biomarkers discussed here and novel markers emerging from discovery investigations [73–76]. However, in GEJ adenocarcinomas (and other solid tumor types), there is a clinical need to use biomarker development methodology to assess combinations of biomarkers, which necessarily complicates clinical protocols. Thus, in GEJ adenocarcinomas, current data suggest that FDG-PET may have utility as a predictive biomarker that has a high negative predictive value (95%) but limited positive predictive value (45%–50%) for histopathological response. These data support investigation in a prospective, randomized, clinical trial in which FDG-PET is used as a predictive biomarker to alter the clinical treatment decision for neoadjuvant therapy (and this study is planned—the European Organization for Research and Treatment of Cancer IMAGE trial). If confirmed, the use of FDG-PET as a predictive biomarker in this way would surpass the current use of therapy based on clinicopathological grounds; there is a clear clinical need to improve the positive predictive value. This implies the need to combine biomarker modalities, for example, with a tissue biomarker (from tumor, serum, or other biospecimen), providing a subclassification of FDG-PET–defined metabolic response to identify which metabolic responders will or will not have a histopathological response. There are several possible permutations of clinical application involving the combined use of a tissue biomarker and/or FDG-PET metabolic response as an imaging predictive biomarker that need to be investigated. One example is the utility of initial subclassification on the

basis of a tumor-measured predictive tissue biomarker and then refinement/modification according to serial FDG-PET-measured metabolic response. Alternatively, the utility of serial tissue biomarker analysis alongside serial FDG-PET would be feasible with a serum biomarker, and there are other combinations that may also be useful and worthy of investigation. Furthermore, ongoing investigation must be set in the context of emerging novel agents and targets for gastroesophageal adenocarcinoma; however, clinical trial design should be able to accommodate this. Nevertheless, data with FDG-PET in chemotherapy versus chemoradiotherapy provide a potential warning regarding generalization to different treatment modalities and the need for optimization of each, which may be a matter of timing of assessment and/or PET technique (tracer or quantification).

It is not yet clear whether the subclassification of GEJ adenocarcinomas into type I, type II, and type III, which have different etiologies, will be relevant to systemic therapy. Nevertheless, emerging data suggest that it will be important for targeted therapies with potentially differential responses in these subtypes, and current clinical protocols have recognized this with subtype-specific inclusion criteria.

PREDICTIVE BIOMARKER DISCOVERY IN EARLY GEJ ADENOCARCINOMAS

This review illustrates the need for ongoing discovery of predictive biomarkers of histopathological response and clinical benefit from distinct combined-modality treatment approaches in early GEJ adenocarcinomas. Molecular biomarker discovery must, to a certain extent, be driven by the requirements of emerging therapeutic targets and novel agents in preclinical and early-phase clinical development. So far, in molecular biomarker discovery in GEJ adenocarcinoma, the emphasis has been on pathway-specific approaches. More recently, hypothesis-generating approaches to discover biomarkers using “omic” platforms were used by Luthra et al. [71] and Greenawalt et al. [72].

These data are promising, and larger scale retrospective evaluation using archived and clinical trial-derived material is needed for hypothesis generation.

Aside from such “blue sky” omic discovery approaches, there are several aspects of current understanding and practice in GEJ adenocarcinomas that would benefit from discovery investigations that have the potential for rapid clinical translation with the application of a hypothesis-testing (as opposed to hypothesis-generating) approach:

- The identification of biological and pathogenic differences among type I, type II, and type III GEJ adenocarcinomas
- The molecular pathways and mechanisms responsible for metabolic and/or histopathological response
- The extent of overlap between molecular mechanisms that define GEJ adenocarcinoma subtypes and metabolic and histopathological response.

Investigational approaches that select patients based on clinicopathological subtypes and that use tissue and imaging biomarkers in the same cohort of patients will be required to address these questions. Serial endoscopic tumor biopsies during therapy are also likely to be important. Data from such investigations should be “back translated” for mechanistic studies in preclinical models to confirm potential leads for predictive biomarkers for prospective evaluation in a combined clinicopathological, imaging, and tissue predictive biomarker strategy for stratified optimal treatment selection in early GEJ adenocarcinomas.

ACKNOWLEDGMENTS

R.D.P. and G.B. are engaged in research in the area of gastroesophageal biomarkers funded by NHS Grampian, Chief Scientists Office, Scotland and the Friends of Aberdeen and the North Centre for Oncology Haematology and Radiotherapy.

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