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Expression Profiling of HER2 and EGFR in Resected Specimens and Plasma Samples from Patients with Esophageal Adenocarcinoma: A Review

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Abstract

HER2 and EGFR are the two receptor tyrosine kinases in esophageal adenocarcinoma for which targeted agents exist, and both are assessed on tissue by convention. The difficulty with tissue in this disease is not the assay but the sampling: alterations are distributed unevenly within a tumour and between primary and metastasis, so one block answers for one place at one time.

Objectives: *To review what has been reported for HER2 and EGFR measured in resected and biopsied tissue against what is recovered from plasma in esophageal and gastroesophageal adenocarcinoma, and to set out the prevalence, the concordance between compartments, and the treatment consequences of each result.*

Material and Methods: *Narrative review of randomised trials, trial biomarker analyses and clinically annotated sequencing cohorts indexed in PubMed and the major oncology journals. Studies were eligible if they reported HER2 or EGFR status in tissue or plasma in esophageal, gastroesophageal junction or gastric adenocarcinoma, matched comparison between compartments, or outcomes stratified by receptor status. No new patient data were generated; all values quoted are those published by the original investigators.*

Results: *In the largest screening dataset available, covering 3,807 samples, HER2 positivity was 22.1 per cent overall but 32.2 per cent in gastroesophageal junction and distal esophageal tumours against 21.4 per cent in gastric tumours, and 31.8 per cent in intestinal-type against 6.1 per cent in diffuse-type disease. Staining was heterogeneous in almost half of cases. Where primary tumour, metastasis and plasma were sequenced in the same patients, only 26 per cent of alterations were identified by all three; restricted to alterations detectable in plasma, circulating tumour DNA recovered 74 per cent against 57 per cent from metastatic and 54 per cent from primary tissue. Among patients amplified by either compartment, matched HER2 inhibition was associated with median overall survival of 26.3 against 7.4 months, and matched EGFR inhibition with 21.1 against 14.4 months. EGFR copy number gain was present in 20 per cent of tumours in a randomised trial population, with amplification in 7.2 per cent.*

Conclusion: *Neither compartment is complete. Tissue defines the protein-level result on which current approvals rest, but samples one region of a heterogeneous tumour; plasma samples the whole disease but only when shedding is sufficient. The published data support using them together rather than choosing between them, particularly for amplification-defined subgroups where the treatment effect is large.*

Abbreviations: *EAC – Esophageal Adenocarcinoma, GEA – Gastroesophageal Adenocarcinoma, GEJ – Gastroesophageal Junction, HER2 – Human Epidermal Growth Factor Receptor 2, EGFR – Epidermal Growth Factor Receptor, IHC – Immunohistochemistry, FISH – Fluorescence In Situ Hybridization, NGS – Next-Generation Sequencing, ctDNA – Circulating Tumour DNA, CNG – Copy Number Gain, OS – Overall Survival, HR – Hazard Ratio.*

Keywords: *HER2; EGFR; Esophageal Adenocarcinoma; Liquid Biopsy; Tumour Heterogeneity*

Introduction

Esophageal adenocarcinoma has proved unusually resistant to targeted treatment. Genomic profiling shows frequent copy number change and considerable mutational complexity, but few recurrent, actionable driver mutations of the kind that transformed treatment in lung cancer [7]. Of the receptor tyrosine kinases, only HER2 has produced an approved agent, and that approval came from a trial conducted largely in gastric rather than esophageal disease [1].

HER2 has been recognised as a driver and prognostic factor in upper gastrointestinal adenocarcinoma for some time [3], and its assessment by immunohistochemistry with reflex in situ hybridization is now routine. EGFR is more widely expressed but has been harder to exploit: it is present in most esophageal tumours

and associated with poor survival, yet phase 3 trials of EGFR inhibitors have been negative overall [5,8].

What both receptors share is a sampling problem. Amplification in this disease is frequently heterogeneous within a single tumour, and the molecular content of a primary tumour and its metastases can differ substantially. A result generated from one resected block or one endoscopic biopsy is therefore a statement about that fragment, not necessarily about the disease. Plasma sequencing offers a different kind of sample, drawn from wherever the tumour is shedding, which raises the question of how the two compare [4].

The aim of this review is to set out what has been measured in each compartment for HER2 and EGFR in esophageal and gastroesophageal adenocarcinoma: how often each alteration is found, how far the two compartments agree, and what treatment consequence follows from a positive result in either.

Material and Methods

Search strategy: PubMed and the archives of the major oncology and gastroenterology journals were searched for studies of HER2 or EGFR in esophageal, gastroesophageal junction and gastric adenocarcinoma. Search terms combined HER2, ERBB2 and EGFR with esophageal adenocarcinoma, gastroesophageal, resected specimen, plasma, circulating tumour DNA, amplification, copy number gain and concordance. Reference lists of retrieved trials and reviews were screened by hand.

Eligibility: Studies were included if they reported the prevalence of HER2 or EGFR alteration in a defined esophageal or gastroesophageal population, matched comparison of the two compartments in the same patients, or clinical outcomes stratified by receptor status. Randomised trials and their prespecified biomarker analyses were included preferentially. Studies confined to squamous cell carcinoma were cited only where they inform assay methodology.

Data extraction and handling: Design, sample size, specimen type, assay platform, reported prevalence and reported effect estimates with their confidence intervals were extracted as published. No pooling or re-analysis was performed and no patient-level data were obtained. Prevalence figures are reported with the assay and scoring criteria attached, because HER2 scoring in this disease differs from breast cancer practice and the two are not interchangeable. Figures 1 to 4 and Tables 1 and 2 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

HER2 prevalence depends on where the tumour is and what type it is: The largest screening dataset in this disease comes from the trial that established trastuzumab in advanced gastroesophageal cancer, in which 3,807 samples were centrally assayed by immunohistochemistry and in situ hybridization in parallel. Positivity, defined as IHC 3+ or amplification, was 22.1 per cent overall. It was substantially higher in gastroesophageal junction tumours than in gastric tumours, at 32.2 against 21.4 per cent, and higher still in intestinal-type disease at 31.8 per cent against 6.1 per cent in diffuse-type (Figure 1) [2]. Rates were similar between European and Asian patients, at 23.6 and 23.9 per cent [2].

The location effect matters for a review concerned with esophageal adenocarcinoma specifically, because it means prevalence figures quoted from gastric series understate what is found in the esophagus and at the junction. It also means that a trial population assembled predominantly from gastric primaries will contain a different proportion of eligible patients than an esophageal one.

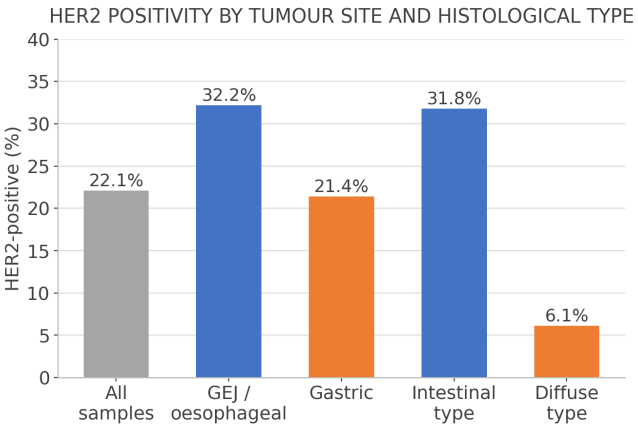

Figure 1: HER2 positivity by tumour site and histological type in 3,807 centrally assayed gastroesophageal samples [2]

Staining is heterogeneous in half of cases: The same screening analysis reported variability in HER2 staining, defined as 30 per cent or fewer stained cells, in almost half of all cases, with the proportion rising in the lower immunohistochemistry categories. Polysomy was present in 4 per cent [2]. Heterogeneity of this degree is not a technical artefact to be corrected; it is a property of the disease, and it is the reason a single block can misclassify a tumour in either direction.

What plasma recovers that tissue does not: The most direct evidence on the two compartments comes from a clinically annotated sequencing cohort of 2,140 plasma tests across 1,630 patients with gastroesophageal adenocarcinoma. In a subset of 34 untreated patients who underwent paired sequencing of the primary tumour, a metastasis and plasma, only 26 per cent of the alterations identified were found by all three methods. Restricting the comparison to alterations detectable in plasma, circulating tumour DNA recovered 74 per cent of them, against 57 per cent from metastatic tissue and 54 per cent from the primary, and three-way agreement rose to 32 per cent (Figure 2) [4].

Among patients found to be HER2-amplified by either tissue or plasma sequencing at any point, universal concordance between methods was 54 per cent [4]. That figure is worth stating plainly: for a marker that determines eligibility for the only approved targeted therapy in this disease, roughly half of positive patients were positive by one method and not the other.

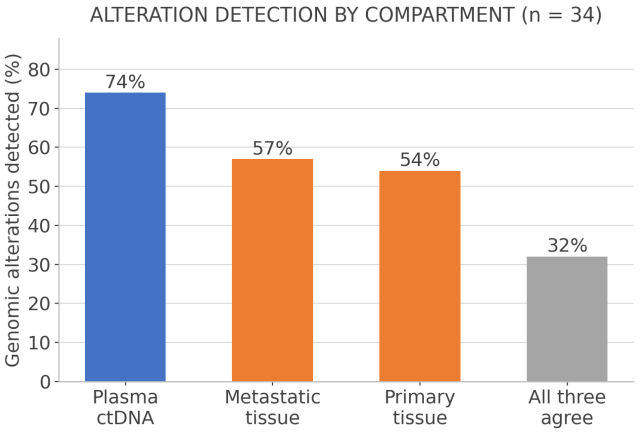

Figure 2: Proportion of plasma-detectable genomic alterations recovered from each compartment in patients sequenced in all three (n = 34) [4]

Study	n	Specimen	Principal reported finding
Bang et al. 2010 [1]	594	Tissue	Trastuzumab improves OS in HER2-positive disease
Van Cutsem et al. 2015 [2]	3,807	Tissue	HER2 positivity 32.2% at the GEJ against 21.4% gastric
Maron et al. 2019 [4]	1,630	Plasma	ctDNA recovers 74% of alterations; 54% HER2 concordance
Dutton et al. 2014 [5]	450	Tissue	Gefitinib improves PFS but not OS overall
Petty et al. 2017 [6]	340	Tissue	EGFR amplification predicts gefitinib benefit

Table 1: Principal studies reviewed, with specimen type and the finding as reported by the original investigators

Amplification found in either compartment predicts benefit: In the same cohort, patients whose tumours were HER2-amplified by plasma sequencing, tissue sequencing or both and who received HER2-directed treatment had a median overall survival of 26.3 months against 7.4 months for those who did not (p = 0.002). The corresponding figures for EGFR-amplified patients receiving EGFR inhibition were 21.1 against 14.4 months (p = 0.01) (Figure 3) [4]. These are non-randomised comparisons and carry the selection effects that implies, but the magnitude of the HER2 difference is larger than treatment effects generally seen in this disease.

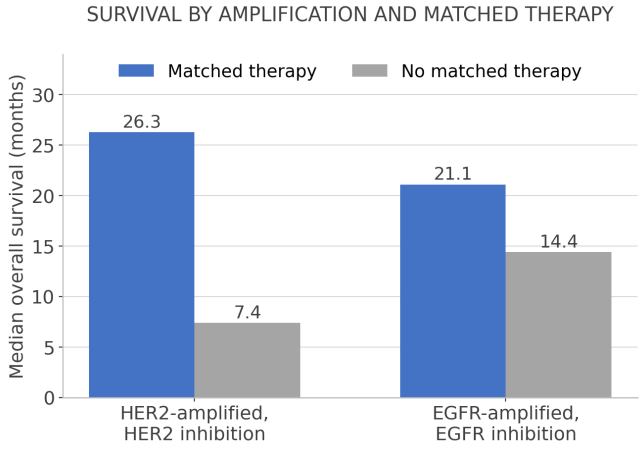

Figure 3: Median overall survival by amplification status and receipt of matched targeted therapy [4]

EGFR: common, prognostic, and only occasionally actionable: EGFR is expressed in most esophageal cancers and its expression is associated with poor survival, while increased copy number occurs in a smaller subset [5,8]. A randomised phase 3 trial of gefitinib against placebo in esophageal cancer progressing after chemotherapy improved progression-free survival and disease control but not overall survival [5]. The prespecified biomarker analysis of that trial changes the reading. Among tumours assessed by in situ hybridization, 20 per cent showed EGFR copy number gain, comprising high polysomy in 13 per cent and amplification in 7.2 per cent. In the amplified subgroup, gefitinib was associated with a hazard ratio for death of 0.21 (95% CI 0.07 to 0.64, p = 0.006), while no difference was seen by EGFR, KRAS, BRAF or PIK3CA mutation status (Figure 4) [6].

This is the pattern that has repeatedly defeated targeted therapy trials in esophageal adenocarcinoma. A negative trial in an unselected population conceals a small subgroup with substantial benefit, and the subgroup is defined by an amplification that a single tissue sample may not capture.

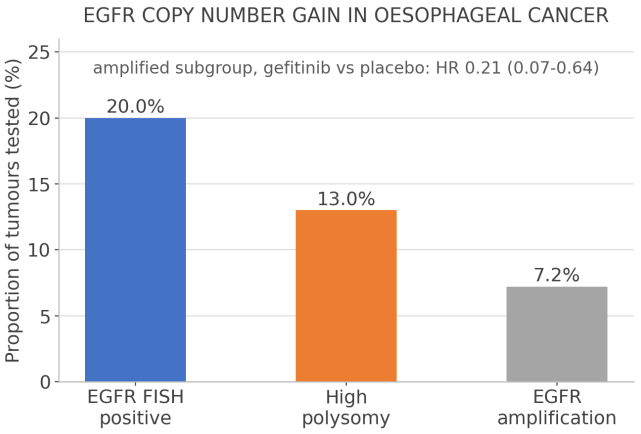

Figure 4: EGFR copy number gain in tumours from a randomised trial population, with the treatment effect in the amplified subgroup [6]

Compartment	What it establishes	Principal limitation
Resected specimen	Protein-level HER2 score on which approvals rest	One region of a heterogeneous tumour [2]
Endoscopic biopsy	Status before any resection exists	Smaller sample, same heterogeneity problem [2]
Metastatic tissue	Status of the disease being treated	Recovered 57% of plasma-detectable alterations [4]
Plasma ctDNA	Composite picture across all shedding sites	Depends on shedding; no protein-level result [4]

Table 2: What each compartment establishes and what it cannot, as reported in the studies reviewed

Discussion

The published data do not support a straightforward ranking of the two compartments. Tissue produces the result that current approvals are written around, and no plasma assay yields a protein-level immunohistochemistry score. But tissue in this disease samples one place at one time, and the heterogeneity data show how consequential that is: staining varied in almost half of centrally assayed cases [2], and where primary, metastasis and plasma were sequenced together, three-quarters of alterations were missed by at least one method [4].

Plasma is not a solution to that problem so much as a different exposure to it. It recovered more alterations than either tissue site in the paired comparison, which is what would be expected from a sample drawn across all shedding lesions rather than one [4]. Its weakness is that recovery depends on shedding, which varies with disease site, tumour burden and timing relative to treatment, so a negative plasma result in low-burden disease carries little information.

Implications for testing

The practical reading is that the two are complementary. For a patient whose tissue is HER2-negative but whose disease behaves aggressively, or where the available block is small or old, plasma sequencing may identify an amplification that the block did not contain. For a patient with plasma-detected amplification and no tissue confirmation, the survival data associated with matched treatment are substantial enough to warrant consideration [4]. Neither substitutes for the other, and reporting one as though it refutes the other misreads what each measures.

For EGFR the implication is narrower. Copy number gain identifies a subgroup of roughly one in five, and amplification a

subgroup of about one in fourteen, in whom an otherwise inactive drug produced a large survival effect [6]. That is an argument for prospective trials in amplification-selected patients, not for using EGFR inhibitors unselected.

Study limitations

The limitations belong to the underlying evidence. The concordance data reviewed here come from a single large cohort, and the triplet-paired subset within it is small at 34 patients [4]. Survival comparisons by receipt of matched therapy are non-randomised, and patients who receive targeted treatment differ systematically from those who do not. The biomarker analysis of the gefitinib trial was prespecified, but the amplified subgroup contained few patients and the confidence interval around the hazard ratio is correspondingly wide [6]. HER2 prevalence figures vary widely across published series depending on assay, antibody and scoring criteria, and figures generated under breast cancer criteria are not comparable with those generated under gastroesophageal criteria [2,3].

Two gaps deserve naming. No randomised trial has yet allocated treatment on the basis of a plasma result in this disease, so the clinical utility of plasma-directed selection remains inferred rather than demonstrated. And the studies reviewed here report esophageal, junctional and gastric primaries together far more often than separately, which limits how precisely any of these figures can be applied to esophageal adenocarcinoma alone.

Conclusion

HER2 is more frequently positive in esophageal and junctional adenocarcinoma than in gastric primaries, and its expression is heterogeneous in a large proportion of cases. EGFR is widely expressed but actionable only in the minority with copy number gain. For both receptors, the limiting factor is not assay performance but which part of the disease was sampled: paired sequencing shows that plasma, primary tumour and metastasis each recover a different and incomplete share of the alterations present. Where amplification is identified in either compartment, matched targeted therapy has been associated with substantially longer survival. Testing both compartments, rather than treating one as the reference standard for the other, is what the published data support.

Acknowledgements

We record our thanks to the investigators behind the cohorts brought together in this article, since their published measurements are what the whole discussion rests upon.

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Conflict of Interest

None of the authors has a competing interest to report.

Ethics Statement

All material behind this article was published beforehand. No patients were enrolled and no new records were opened, so the work falls outside the remit of ethical review.

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