Meta-analysis

Forthcoming prognostic markers for esophageal cancer: a systematic review and meta-analysis

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Background: The incidence of esophageal cancer is rising, and survival rates remain poor. This meta-analysis summarizes five molecular mechanisms of disease progression, which are related to prognosis.

Patients and methods: A systematic search was conducted using MEDLINE, PubMed, EMBASE, Current Contents Connect, Cochrane library, Google Scholar, Science Direct, and Web of Science. Original data was abstracted from each study and used to calculate a pooled event rate and 95% confidence interval (95% CI).

Results: Our analysis included five octamer-binding transcription factor 4 (OCT4) studies (564 patients), six sex determining region Y-box 2 (SOX2) studies (336 patients), five oestrogen receptor (ER) studies (367 patients), seven MET or MNNG HOS Transforming gene (c-Met) studies (1,015 patients) and six insulin like growth factor receptor studies (764 patients). Incidence of OCT4 in SCC was 53.60% (95% CI: 0.182-0.857) and the overall hazard ratio for poor clinic outcome was 2.9 (95% CI: 1.843-4.565). The incidence of SOX2 in SCC was 69.2% (95% CI: 0.361-0.899) however, was associated with significant heterogeneity of 90.94%. The prevalence of Oestrogen receptor α and β in SCC were 37.90% (95% CI: 0.317-0.444) and 67.20% (95% CI: 0.314-0.901) respectively. The prevalence of MET in EAC was 33.20% (95% CI: 0.031-0.884) and the incidence of insulin-like growth factor-1 receptor (IGF-1R) in EAC was 67.70% (95% CI: 0.333-0.898).

Conclusions: Our results show that the status of ER, OCT4 and SOX2 expression correlates with the unfavourable prognosis in patients with esophageal squamous cell carcinoma (ESCC). This study also highlights the potential impact of the IGF-1R on the biology of EAC and the expression of Met was recognised as a significant prognostic factor. Our data supports the concept of IGF axis, ER, Met, OCT4 and SOX2 inhibition as (neo-) adjuvant treatment.

Keywords: Esophageal cancer; insulin-like growth factor axis (IGF axis); oestrogen receptors (ER); MET or MNNG HOS Transforming gene (c-Met); octamer-binding transcription factor 4 (OCT4); sex determining region Y-box 2 (SOX2)

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Introduction

The incidence and mortality from cancer of all types in the United States has decreased during the 1991-2006 timeframe (1). However, the opposite is true for esophageal cancer. Its incidence and mortality continue to rise. In 2010, estimated new cases of esophageal cancer number 16,640 in the United States, while deaths total 14,500 (1). The United States has seen an average increase of 20.6% per year in the incidence of adenocarcinoma of the esophagus since that time (2). It is projected that there will be 16,470 new patients diagnosed with esophageal cancer and 14,280 deaths from it in 2008 (1).

Esophageal cancer is a highly lethal disease in which only one-third of patients present with resectable disease. Of this select group, the average 5-year survival is only 35-45% (3). Another consideration is our less-than-satisfactory ability to predict particular tumour's response to neoadjuvant therapy. Targeted molecular therapy in upper gastrointestinal cancer has become an increasingly popular topic over the past few

years. In part, this is due to rapid advances in our capability to characterize tumour biology. In esophageal cancer, VEGF (4), E-cadherin (5), COX2 (6), Survivin (7), EGFR (8) and HER2 (9) have been thoroughly investigated in the past with the help of a meta-analysis. However, insulin-like growth factor axis (IGF axis), oestrogen receptors (ER), MET or MNNG HOS Transforming gene (c-Met), octamer-binding transcription factor 4 (OCT4) and sex determining region Y-box 2 (SOX2) have not been examined.

Current concepts suggest that centrally deposited fat, so-called visceral adipose tissue, is more metabolically active than peripheral subcutaneous fat, and a more significant fuel for the association with dysmetabolism and related problems, including cancer (10). The IGF axis is thought to play a role in the link between obesity and cancer (11). The observation that insulin resistance is associated with an increased risk of cancer has led to the hypothesis that this may be mediated through the IGF axis (12,13).

One promising subset may include tumours with MET gene amplification resulting in overexpression and constitutive activation of the encoded receptor tyrosine kinase MET (14,15). In a large-scale preclinical screening approach, previously MET amplification in approximately 20% of gastric cancer cell lines and have demonstrated that this amplification confers extraordinary susceptibility to apoptosis induction by the selective MET inhibitor PHA-665752 (Pfizer, La Jolla, CA) (16). Recently, crizotinib (PF-02341066, Pfizer) was identified as an orally bioavailable, potent, ATP-competitive small-molecular inhibitor of the catalytic activity of MET kinase (17,18).

Sox2 is an important member of the Sox gene family. Sox (SRY box) genes have been identified through their homology to the high mobility group (HMG) box (79 amino acids) of sex-determining factor SRY (19-22). The Sox genes encode transcription factors that interact with DNA through their highly conserved HMG domain (23,24). The Sox genes are expressed in a wide variety of tissues, and play important roles in the regulation of organ development and cell type specification (20,22). It has been found that amplification at the chromosomal region 3q26 occurs frequently in esophageal squamous cell carcinoma (ESCC) and that SOX2 within the 3q26 amplicon is amplified and overexpressed (25).

OCT4, also known as OCT3, belongs to the POU (Pit-Oct-Unc) transcription factor family (26). The POU family of transcription factors can activate the expression of their target genes through binding the octameric sequence motif with an AGTCAAAT consensus sequence (27,28). The expression of this gene is necessary for the maintenance of pluripotentiality in embryonic stem cells (ESCs) and primordial germ cells and is down-regulated in all differentiated cells *in vitro* as well as *in vivo* (28).

The striking 3-4: one male predominance of ESCC has been observed in areas (29,30). The molecular mechanisms for such distinct gender difference in term of mortality rate and prognosis are not clear. Sex hormones, especially the typical type of oestradiol/oestrogen, and their respective receptors have been speculated to be crucial determinants for sex-related susceptibility to cancer. Oestrogen and progesterone receptors (ER and PR) are over-expressed in EC tissue whereas absent in mature normal esophageal mucosa of the foetus (31). Inhibitory effect by oestrogen on ESCC growth and development has been observed in mouse ESCC model (32). Studies on breast and endometrial cancers have shown that there are two different isoforms of human ER, i.e., ERα and ERβ, both of which are receptors for oestradiol. Recent studies have indicated that ERα expression is an unfavourable prognostic indicator in ESCC (33).

The aim of this meta-analysis was to summarize these five molecular mechanisms of disease progression, which are related to prognosis.

Methods

Study protocol

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses PRISMA guidelines where possible in performing our systematic review (34). We performed a systematic search through MEDLINE (from 1950), PubMed (from 1946), EMBASE (from 1949), Current Contents Connect (from 1998), Cochrane library, Google scholar, Science Direct, and Web of Science to May 2013. The search terms included "esophageal cancer", "SOX2, OCT4, MET, IGF and oestrogen", which were searched as text word and as exploded medical subject headings where possible. No language restrictions were used in either the search or study selection. The reference lists of relevant articles were also searched for appropriate studies. A search for unpublished literature was not performed.

Study selection

We included studies that met the following inclusion criteria:

- Studies identifying the population of patients with

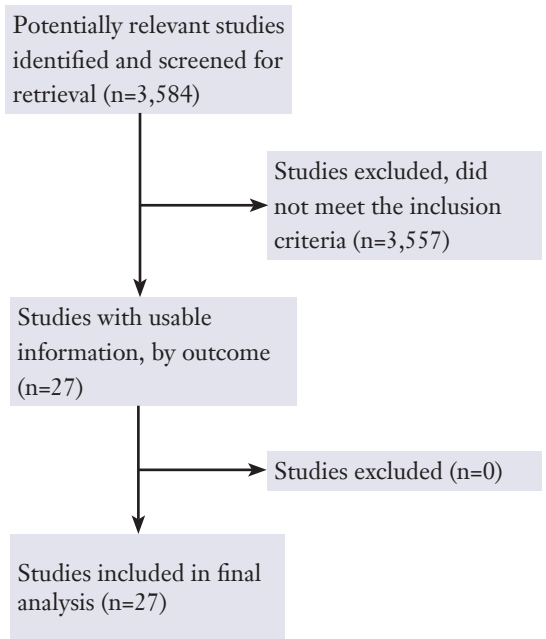

Figure 1 Flow of included studies.

esophageal cancer;

- Studies dealing with the association between SOX2, OCT4, MET, insulin like growth factor receptor and oestrogen with esophageal cancer.

Data extraction

We performed the data extraction using a standardized data extraction form, collecting information on the publication year, study design, number of cases, total sample size, population type, country, continent, mean age and clinical data. The event rate and confidence intervals were calculated.

Statistical analysis

Pooled event rate and 95% confidence intervals were using a random effects model (35). We tested heterogeneity with Cochran's Q statistic, with P<0.10 indicating heterogeneity, and quantified the degree of heterogeneity using the I^2 statistic, which represents the percentage of the total variability across studies which is due to heterogeneity. I^2 values of 25%, 50% and 75% corresponded to low, moderate and high degrees of heterogeneity respectively (36). The quantified publication bias using the Egger's regression model (37), with the effect of bias assessed using the fail-safe number method. The fail-safe number was the number of studies that we would need to have missed for our observed result to be nullified to statistical non-significance at the P<0.05 level. Publication bias is generally regarded as a concern if the fail-safe number is less than 5n+10, with n being the number of studies included in the meta-analysis (38). All analyses were performed with Comprehensive Meta-analysis (version 2.0).

Results

The original search strategy 3,584 retrieved studies (*Figure 1*). The abstracts were reviewed and articles were selected for full-text evaluation. Of the articles selected, only 27 studies (12,484 patients) met full criteria for analysis and are summarised in *Table 1*. This included five OCT4 studies (564 patients), six SOX2 studies (336 patients), five oestrogen receptor studies (367 patients), seven MET studies (1,015 patients) and 6 Insulin like growth factor receptor studies (764 patients). The years of publication ranged from 1990 to 2012.

The incidence of OCT4 in SCC was 53.60% (95% CI: 0.182-0.857) and the overall hazard ratio for poor clinic outcome was 2.9 (95% CI: 1.843-4.565). The incidence of SOX2 in SCC was 69.2% (95% CI: 0.361-0.899) however, was associated with significant heterogeneity of 90.94%. The prevalence of ER α and β in SCC were 37.90% (95% CI: 0.317-0.444) and 67.20% (95% CI: 0.314-0.901) respectively. The prevalence of MET in EAC was 33.20% (95% CI: 0.031-0.884) and the incidence of insulin-like growth factor-1 receptor (IGF-1R) in EAC was 67.70% (95% CI: 0.333-0.898).

Heterogeneity and publication bias

The heterogeneity of outcomes has been summarized in *Table 2*. The reason for significant heterogeneity may be attributed to different population groups. No publication bias was detected using the Egger's regression model.

Discussion

Esophageal cancer is one of the most aggressive neoplasms and the overall prognosis for esophageal cancer patients is poor (64). One of the reasons for the low survival rate is the tumour's intrinsic resistance to many clinical therapies, especially chemotherapy. Chemotherapy often removes the bulk of a tumour mass without preventing tumour recurrence, suggesting the

Table 1 Characteristic of the studies included in the systematic review

Author	Biomarker	Tumour type	Country	Year	Patients
Li *et al.* (39)	OCT4	ESCC	China	2012	50
Wang *et al.* (40)	SOX2 and OCT4	ESCC	Norway	2009	162
He W *et al.* (41)	OCT4	ESCC	China	2012	153
Zhou Xi *et al.* (42)	OCT4	ESCC	China	2011	174
Bass *et al.* (43)	SOX2	ESCC	U.S.A	2009	40
Bahl *et al.* (44)	SOX2 and OCT4	ESCC	India	2012	25
Saigusa *et al.* (45)	SOX2	ESCC	Japan	2011	20
Gen *et al.* (25)	SOX2	ESCC	Japan	2010	40
Long *et al.* (46)	SOX2	ESCC and EAC	USA	2009	49
Nozoe *et al.* (33)	Oestrogen receptors α and β	ESCC	Japan	2007	73
Liu *et al.* (47)	Oestrogen receptor β	EAC	USA	2004	27
Wang *et al.* (48)	Oestrogen receptor β	ESCC	China	2011	132
Kalayarasan *et al.* (49)	Oestrogen and progesterone receptors	ESCC and EAC	India	2008	45
Zuguchi *et al.* (50)	Oestrogen receptors α and β	ESCC	Japan	2012	90
Saeki *et al.* (51)	C-MET	ESCC	Japan	2002	76
Tuynman *et al.* (52)	C-MET	EAC	The Netherlands	2008	145
Houldsworth *et al.* (53)	C-MET	EAC	USA	1990	1
Porte *et al.* (54)	C-MET	ESCC and EAC	Italy	1998	36
Anderson *et al.* (55)	C-MET	EAC	UK	2006	72
Lennerz *et al.* (56)	C-MET	EAC	USA	2011	489
Kato *et al.* (57)	C-MET	ESCC	Japan	2013	196
Imsumran *et al.* (58)	IGF-Ir	ESCC	USA	2007	100
Donohoe *et al.* (59)	IGF-Ir	EAC	Ireland	2012	220
Doyle *et al.* (60)	IGF-Ir	EAC	Ireland	2012	124
Kalinina *et al.* (61)	IGF-Ir	EAC	Germany	2010	234
Iravani *et al.* (62)	IGF-Ir	EAC	USA	2003	34
Zhao *et al.* (63)	IGF-Ir	EAC	Canada	2009	52

Table 2 Overall odds ratio and 95% CI for patient outcomes

Outcome	Event rate (%)	95% CI	I^2	P value
Incidence of OCT4 in SCC	53.6	0.182-0.857	97.65	<0.001
OCT4 pooled hazard ratio	2.9	1.843-4.565	0.00	0.51
Incidence of SOX2 in SCC	69.2	0.361-0.899	94.37	<0.001
Incidence of oestrogen receptor β in SCC	67.2	0.314-0.901	94.88	<0.001
Incidence of oestrogen receptors α in SCC	37.9	0.317-0.444	0.00	0.41
Incidence of MET in EAC	33.2	0.031-0.884	98.81	<0.001
Incidence of IGF-1R in EAC	67.7	0.333-0.898	89.87	<0.001

survival of a subset of cancer stem cells. Studies have provided experimental evidence for the concept that human tumour growth may depend on a small portion cancer stem cells (65).

SOX2 and OCT4

The expressions of Oct3/4 and Sox2 were firstly discovered in human esophageal squamous cancer cell lines with the

antibody AF1759 and MAB2018 from R&D System for immunocytochemistry. Among 153 specimens from the department of Oncology at Zhengzhou University (66), 105 (68.7%) were negative or weakly positive for OCT4 staining; 21 (13.7%) were moderately positive and 27 (17.6%) were strongly positive. Higher expression level of OCT4 was significantly associated with higher histological grade (P<0.001), indicating its correlation with dedifferentiation of these tumours. The median follow-up time for the 56 patients still alive was 124 months (range, 118-155 months) and for the remaining 97 patients who died during the follow-up period was 61 months (range, 1-139 months). In univariate analysis, patients with low OCT4 expression level in tumours had a better overall survival than patients with tumour showing moderate or high OCT4 expression level (P=0.002 and P<0.001), respectively. Zhou *et al.* (42) Oct4 protein was expressed in most (93.7%) ESCC samples but it was not observed in esophageal mucosa. The over-expression of Oct4 in ESCCs suggests that it is a potential target for ESCC therapy. Oct4 could be a useful tumour marker in an immunohistochemical panel designed to differentiate between ESCC and esophageal mucosa. Expression of Oct4 in tumorospheres might indicate the presence of a population of ECSCs and its expression in xenograft tumours suggests that Oct4 is also associated with tumour metastasis. SOX2 gene is an amplification target of 3q26.3 in ESCC, and that SOX2 promotes ESCC cell proliferation *in vitro* (25). LY294002, an inhibitor of phosphatidylinositol 3-kinase, and rapamycin, an inhibitor of mTORC1, suppressed the ability of SOX2 to enhance proliferation of ESCC cells *in vitro*. Effects of SOX2 knockdown, including reduced levels of phosphorylated AKT and decreased ESCC cell proliferation, were reversed with constitutive activation of AKT with knockdown of phosphatase and tensin homolog. In mouse xenografts, SOX2 promoted *in vivo* tumor growth of ESCC, which was dependent on AKT/mTORC1 activation. LY294002 suppressed the ability of SOX2 to enhance tumor growth of ESCC by reducing cell proliferation, but not by enhancing apoptosis. These findings suggest that SOX2 promotes *in vivo* tumor growth of ESCC through activation of the AKT/mTORC1 signaling pathway, which enhances cell proliferation (67).

Wang *et al.* (40) established that Sox2 expressions were significantly associated with higher histological grade (P<0.001 for both factors), indicating their correlation to dedifferentiation in these tumours and a significant correlation between increasing levels of Sox2 immunostaining and decreasing survival for the patients (P<0.001) was observed. After being stratified by histological grade, Sox2 expressions were still significantly associated with unfavourable overall survival (P=0.008 and P=0.003, respectively).

The role of OCT4 & Sox2 in esophageal carcinogenesis evidences further studies.

Oestrogen receptor

Oestrogens, the primary female sex hormones, are mechanistically linked to aspects of cancer risk and cancer development. A connection between oestrogen-activated signalling and carcinogenesis in many organs, including mammary glands (68), ovaries and colon (69) has been clearly defined, although it is unclear whether a similar connection exists for the esophagus, and esophageal adenocarcinoma in particular. Furthermore, oestrogen is actively involved in the regulation of metabolism in adipose tissues (70), and it can be synthesized locally by activated aromatase in adipocytes in both men and women (71). Therefore it seems reasonable to consider that oestrogens might contribute towards the gender difference for esophageal adenocarcinoma. Involvement of oestrogen signalling in regulation of adipose tissue metabolism indicates a possible connection between the effects of oestrogen and male obesity-one of the main risk factors for esophageal adenocarcinoma.

A recent article from Japan (50) ERα immunoreactivity was detected in the nuclei of carcinoma cells in 38/90 ESCC ERβ immunoreactivity was detected in the nuclei of carcinoma cells with a variety of immunointensity in 88/90 ESCC. Correlation between the status of ERβ immunoreactivity and clinicopathological variables in 90 ESCC patients There was a statistically significant positive association between ERβ H score and tumor differentiation (P=0.0403) and TNM-pM (LYM) (P=0.0164). There was also a weak but statistically significant positive correlation between the ERβ H score and Ki67/MIB1 LI (P=0.0497, r=0.207). No significant association was detected between ERβ immunoreactivity and age, gender, tumor size, depth of tumor invasion, presence of lymph node metastasis, TNM stage, lymphatic invasion, venous invasion or infiltrative growth pattern of the patients examined in the present study.

The patients with positive nuclear ERα immunoreactivity in carcinoma cells were by no means associated with better survival or favorable clinical outcome (log-rank test: OS,

P=0.4660; DFS, P=0.3468). In the present study, the patients with high nuclear ERβ immunoreactivity were significantly associated with shorter survival or adverse clinical outcome (log-rank test: OS, P=0.0017; DFS, P=0.0005). Results of univariate analysis (*Table 2*) demonstrated that pathological stage (OS, P=0.0003; DFS, P=0.0006), ERβ status in the nucleus of carcinoma cells (OS, P=0.0025; DFS, P=0.0010), tumor size (OS, P=0.0485; DFS, P=0.0366) and infiltration type (OS, P=0.0200; DFS, P=0.0416) were all significant prognostic factors for OS and/or DFS in 90 ESCC examined in our study. A subsequent multivariate analysis did reveal that ERβ status (OS, P=0.0010; DFS, P=0.0007) was an independent prognostic factor for OS and DFS of these patients, as well as pathological stage (OS, P=0.0019; DFS, P=0.0091) and infiltration type (OS, P=0.0185; DFS, P=0.0328).

Future perspective would be if a confirmed link might provide support for ERβ to be used as a target for therapy, or as a prognostic marker.

Met expression and esophageal adenocarcinoma

The Met receptor is a tyrosine kinase receptor, the product of a proto-oncogene (72). It acts as a receptor for hepatocyte growth factor (HGF), a potent mitogen and pro-motility agent for epithelial cells (73,74). HGF is primarily produced by mesenchymal cells to act on Met-expressing epithelial cells in a paracrine fashion (75).

The predominant adhesion protein of epithelial tissue is E-cadherin (13), and this is down-regulated in esophageal cancer (76). E-cadherin binds to β-catenin at the cell membrane and is linked to the control of β-catenin—regulated transcription (77,78). The β-catenin protein is found in three cellular pools: membranous, cytoplasmic, and nuclear. The translocation among these is tightly regulated (79), and the dynamic equilibrium determines the signaling role (80). Nuclear β-catenin is seen in esophageal tumorigenesis (81), and many catenin target genes show increased expression (82,83). Studies have shown an association between HGF/Met stimulation and increased phosphorylation of β-catenin in cell lines (84-86).

Studies of the expression of Met in esophageal malignancy showed increased expression in tumors compared with normal mucosa (51,77,87). Met activation in esophageal cancer induces changes consistent with early invasion, such as down-regulation of E-cadherin, increased nuclear TCF/β-catenin signaling, and anchorage-independent growth. The expression of Met in esophageal adenocarcinoma is associated with a poorer prognosis *in vivo* (55).

The crizotinib expanded phase I cohort study was performed by Massachusetts General Hospital/Harvard Medical School (56). Ten (2%) of 489 patients screened harbored MET amplification; 23 (4.7%) harbored EGFR amplification; 45 (8.9%) harbored HER2 amplification; and 411 (84%) were wild type for all three genes (i.e., negative). MET-amplified tumors were typically high-grade adenocarcinomas that presented at advanced stages (5%; n=4 of 80). EGFR-amplified tumors showed the highest fraction of squamous cell carcinoma (17%; n=4 of 23). HER2, MET, and EGFR amplification were, with one exception (MET and EGFR positive), mutually exclusive events. Survival analysis in patients with stages III and IV disease showed substantially shorter median survival in MET/EGFR-amplified groups, with a rank order for all groups by median survival (from most to least aggressive): MET (7.1 months; P<0.001) less than EGFR (11.2 months; P=0.16) less than HER2 (16.9 months; P=0.89) when compared with the negative group (16.2 months). Two of four patients with MET-amplified tumors treated with crizotinib experienced tumor shrinkage (-30% and -16%) and experienced progression after 3.7 and 3.5 months. MET amplification defines a small and aggressive subset of GEC with indications of transient sensitivity to the targeted MET inhibitor crizotinib (PF-02341066).

These efforts suggest that implementation of larger-scale, genome-wide assays—which would include assessment of MET copy number as well as other infrequent gene amplifications—may be an effective approach to identify multiple rare subgroups that might benefit from targeted therapies.

Insulin like growth factor axis and esophageal adenocarcinoma

Insulin resistance leads to reduced levels of IGF binding proteins and results in a subsequent increase in free IGF-1 (88). Prospective studies have shown a relationship between circulating IGF-1 and the risk of developing prostate, breast, colorectal and other cancers (12). The IGF-1R plays a role in the establishment and maintenance of cellular transformation (89), and the receptor or its ligands may be overexpressed in human tumours (90,91). Its action may protect against apoptosis, and favours invasion and metastasis (92,93).

Howard *et al.* (94) stated that 91% of patients with esophageal adenocarcinoma expressed leptin receptor (ObR), 95% expressed adiponectin receptors 1 (AdipR1)

and 100% expressed adiponectin receptors 2 (AdipR2). Relative expression of ObR was upregulated in 67%, and AdipR1 and AdipR2 were downregulated in 55% and 68% respectively, relative to the calibrator sample. Upregulated ObR and AdipR2 expression was significantly associated with anthropometric and radiological measures of obesity. Upregulated ObR was associated with advanced tumour and node category (P=0.036 and P=0.025, respectively), and upregulated AdipR2 with nodal involvement (P=0.037).

Studies *in vitro* support a role for the IGF axis in esophageal adenocarcinoma progression. Blockade of the IGF-1R leads to apoptosis (95) and IGF-1 stimulates proliferation (62). In esophageal cancer, overexpression of IGF-1R has been associated with the malignant progression of Barrett's esophagus to adenocarcinoma (96).

Trinity College (60) reported that higher IGF-1R protein expressions were observed in SCC cells compared with esophageal adenocarcinoma cells however only adenocarcinoma cell lines significantly increased proliferation in response to IGF-1 (P<0.01). Serum IGF-1 levels were highest in esophageal adenocarcinoma patients (P<0.01) and higher in viscerally obese vs. nonobese (P<0.05) patients. In resected esophageal cancer, increased expression of IGF-1R was observed in the tumor and invasive edge compared with tumor associated stroma (P<0.05), which coincided with increased CD68+ cells in stromal tissue surrounding invasive tumor edge (P<0.01).

A total of 220 patients were studied by Donohoe *et al.* (59). Total and free IGF-1 levels were significantly increased in the serum of viscerally obese patients. Gene expression analysis revealed a significant association between obesity status and both IGF-1R (P=0.021) and IGF-1 (P=0.031) in tumours. TMA analysis demonstrated that IGF-1R expression in resected tumours was significantly higher in viscerally obese patients than in those of normal weight (P=0.023). Disease-specific survival was longer in patients with negative IGF-1R expression than in those with IGF-1R-positive tumours (median 60.0 versus 23.4 months; P=0.027). This highlights the relationship between IGF axis with visceral obesity, and a probable impact on the biology of esophageal adenocarcinoma through its receptor.

Studies are ongoing with other novel agents targeting insulin like growth factor receptor, its ligand IGF-1, and telomerase enzyme (97).

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