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ORIGINAL ARTICLE

Undervalued Criteria in the Evaluation of Multimodal Trials for Upper GI Cancers

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Global economies and their health systems face a huge challenge from cancer: 1 in 3 women and 1 in 2 men will develop cancer in their lifetime. In the less developed countries, the volume of cancer patients will overwhelm the existing healthcare systems. Even in developed regions, patients with upper gastrointestinal (GI) cancer usually present with locally advanced tumors that their prognosis is poor. A detailed knowledge of anatomy, embryology, epidemiology, tumor classifications and tumor growth is key understanding and evaluating the relevant research. We review undervalued criteria necessary to evaluate the response to multimodal therapy for upper GI cancers.

Keywords: Upper gastrointestinal tract, Esophageal carcinoma, Anticancer therapy, Neoadjuvant therapy, Multimodal therapy

INTRODUCTION

The importance of some criteria that are relevant for evaluating the response to drugs used in clinical trials for gastrointestinal (GI) cancers is underestimated. A detailed knowledge of epidemiology, embryology, tumor growth, and the available multimodal therapies is fundamental for evaluating upper GI cancers and monitoring their response to treatment. Here we review those undervalued criteria we deem necessary as the bases for evaluating and monitoring response to anticancer therapy in upper GI cancers.

EVIDENCE

Histology and clinical classifications

An understanding of embryology is key to an understanding of the differential histopathology of upper GI carcinomas, both esophageal and gastric. The fact that cells that develop carcinoma in the upper two-thirds of the esophagus, above and at the levels of the tracheal bifurcation, are in the majority squamous, and those from the lower esophageal third are adenocarcinomas (AC), derives directly from the distinct embryological origin. The differences in esophageal and gastric embryology lead to the dissimilar histopathology. Thus, they influence such details as local and distant tumor spread, treatment options, epidemiological bases, and patient-specific outcomes (1, 2). Esophageal AC and esophageal squamous cell carcinomas (ESCC) comprise about 95% of the combined esophageal tumors and AC of the gastric region. The different classifications of these upper GI cancers, which are based on the clinical, morphological, and anatomical differentiation of the subtypes in the upper GI system, are described later:

1. Esophageal squamous cell carcinoma (ESCC);
2. Esophageal adenocarcinoma (equivalent to AC, adenocarcinoma of the esophagogastric junction (AEG) Type I, according to Siewert (3));
3. Carcinomas of the cardia (AEG Type II) (3);
4. Gastric carcinomas (including subcardial AEG Type III (3)).

Additionally, the Lauren classification differentiates the intestinal (often found in the elderly and in woman, characterized by well differentiated slow-growing cancer cells, which tend to form glands) from the diffuse (found more often in younger patients, equally in men and woman, characterized by poorly differentiated tumor cells that are aggressive and metastasize) and the mixed type (which exhibit both intestinal and diffuse growth patterns) (4).

The complete histological classification includes also other variants of epithelial tumors: variants of squamous cell carcinomas (spindle cell carcinoma, pseudosarcoma, and carcinosarcoma), verrucous carcinoma, *in situ* carcinoma,

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adenoid cystic carcinoma (cylindroma), mucoepidermoid carcinoma, adenosquamous carcinoma, carcinoids, and small cell carcinoma. The variants of non-epithelial tumors include leiomyosarcoma, malignant melanoma, rhabdomyosarcoma, myoblastoma, choriocarcinoma, and lymphoma (5).

Esophageal tumors are further subdivided, according to their anatomical location in the tracheal bifurcation, into the following (6):

1. Cervical esophageal tumors, located between the cricopharyngeal muscle and the suprasternal notch.
2. Suprabifurcal esophageal tumors
   (a) located in the upper thoracic esophagus between the suprasternal notch and the azygos vein
   (b) located at the level of the bifurcation (= ad bifurcationem) between the azygos vein and the inferior pulmonary veins.
3. Infrabifurcal esophageal tumors.

Additionally, AC of the distal esophagus and the esophagogastric junction have been classified based on morphology and anatomical location of the tumor center according to the *Siewert's* classification of adenocarcinoma of the esophagogastric junction, AEG-tumors, which have been approved by the International Gastric Cancer Association (IGCA) and the International Society of Diseases of the Esophagus (ISDE) Consensus Conferences (IGCA-ISDE) (3):

1. AEG Type I tumor: adenocarcinoma of the distal esophagus, which usually arises from an area with specialized intestinal metaplasia of the esophagus (i.e., Barrett's esophagus) and which may infiltrate the esophagogastric junction (EGJ) from above
2. AEG Type II tumor: true carcinoma of the cardia arising from the cardiac epithelium or short segments with intestinal metaplasia at the EGJ, often referred to as a "junctional carcinoma" or "cardia carcinoma"
3. AEG Type III tumor: subcardial gastric carcinoma that infiltrates the EGJ and the distal esophagus from below

The various reasons that justify this classification have been previously reported (3, 7). When using the Siewert's classification, one must use the endoscopic definition of the cardia—the proximal margin of the longitudinal gastric mucosal folds—and not the Z-line (8). Gastric cancer is anatomically divided into thirds: the upper, the middle, and the lower stomach (7). Therefore, the subcardial AEG Type III is, anatomically, an upper gastric cancer.

Esophageal tumors are usually further differentiated in terms of the local depth of the tumor invasion (6, 7): (1) Early tumors (T1 and T2 tumors) and (2) Locally advanced tumors (cT3/4 and cN0/+). In contrast, the Japanese Gastric Cancer Association classification defines any early gastric cancer as a T1 tumor, irrespective of any lymphatic spread (7). Mucosal tumors are designated M (T1a) and submucosal as SM (T1b).

Epidemiology

Cancer is a major problem in the United States: 1 in 3 women and 1 in 2 men will develop cancer in her or his lifetime (9). The American Cancer Society (ACS) and the National Cancer Institute (NCI) have estimated the prevalence of cancer survivors for January 1, 2012 and January 1, 2022, by cancer site. Based on the National Cancer Database and the SEER-Medicare Database, the evidence showed that 13.7 million Americans with a history of cancer were alive on January 2012 and that this value would increase to nearly 18 million by January 2022 (9). In 1970, only a calculated 660,000 patients in the United States developed cancer (10).

Regardless of etiology, the incidence of esophageal carcinomas is rising. For 2005, in the United States, 14,520 new cases and 13,570 deaths were reported (11) versus an estimate for 2013 of almost 18,000 new cases with an estimated death rate of more than 15,000 (12). Barrett's metaplasia alone cannot explain the increase, as it has just a 2% mortality rate within 10 years of diagnosis in a population-based trial, and some of those patients die from comorbidities (13).

The proportion of new cancer cases diagnosed in less developed countries is projected to increase from about 56% of the world total in 2008 to more than 60% in 2030 (14, 15). According to the ACS, an estimated 38% of patients with non-metastasized localized esophageal carcinoma survive for 5 years, compared to just 20% of those that present with regional spread and only 3% of those with a distant tumor traced to an esophageal origin (16). Five-year survival rates for gastric carcinomas are stage-dependent (16): Stage IA, 71%; Stage IB, 57%; Stage IIA, 46%; Stage IIIA, 20%; Stage IIIB, 14%; Stage IIIC, 9%; and Stage IV, 4%. Although they were based on the old Union for International Cancer Control (UICC) classification then in use, the Japanese survival data are nearly up to 20% superior in every tumor category: Stage IA 92.2%, Stage IB 85.3%, Stage II 72.1%, Stage IIIA 52.8%, Stage IIIB 31%, and Stage IV 14.9% (17). One reason for this significant difference might be that U.S. surgeons prefer a limited D0/1 lymphadenectomy, although the D2-lymphadenectomy is associated with a lower loco-regional recurrence and cancer-related death than those associated with D0/1 (18).

An increase of the incidence of esophageal cancers was reported in 1999 in both histological subtypes, AC and esophageal squamous cell carcinomas (ESCC) (19). Another report on all cancer sites noted a disparity shift: cancer incidence and mortality were "*. . . lower in other racial and ethnic groups than in Whites and African-Americans*". Additionally, locally advanced tumor categories were more likely to be diagnosed in minority populations than in Whites (20). Others report incidences that are dependent on histological type (21). They note, as well, that because ESCC is steady or slightly decreasing the increase in the incidence of esophageal cancer reflects primarily an increase in AC (21–25). So far, the reasons for the increase in AC remain unclear (26). A recent study reported on a cohort trial selected from patients with GERD. This largest electronic database of longitudinal care compared patients with Barrett's metaplasia (1,677), with esophagitis (6,392), simple reflux (6,328), and with a reference cohort (13,416). It projected that 2% would die of Barrett's adenocarcinoma (AEG Type I) during a 10-year period, and it showed that

patients with Barrett's esophagus more frequently died from comorbidities such as ischemic heart disease than from cancer (27). These data suggest that acid reflux alone cannot be the sole reason for the increased incidence of adenocarcinoma of the EGJ. As the population ages, it may be expected that EG junction cancers would also increase.

The fact that, in China, Barrett's carcinoma is both a very uncommon and a stable disease (28) suggests that dietary and lifestyle choices contribute. Morbid obesity is associated with a greater rate of reflux in the elderly, and morbidly obese patients also exhibit elevated reflux (29–31). Obesity has been identified as an independent risk factor for the development of GERD (32, 33). Additionally, of morbidly obese patients who underwent endoscopy, at least one pathological finding was seen in approximately 80%, despite the fact that the patients were asymptomatic (34). Morbid obesity might be an important factor in the development of Barrett's cancer, as this tumor is rare in Southeast Asia, where morbid obesity is less prevalent than it is in Western countries (35). Interestingly, Asian populations have also been shown, at a body mass index (BMI) inferior to that of Western patients, to have an elevated risk of type 2 diabetes and other co-morbidities (35). It can be assumed that, as the incidence of morbid obesity increases with the burgeoning rise of the middle class in China and India (36), Barrett's metaplasia will increase across Asia in parallel.

Since its discovery, *Helicobacter pylori* (37) has been accepted as the most important risk factor for gastric adenocarcinoma (38). While *H. pylori* infection in Asia has been reported to engender more intense chronic inflammation and neutrophil activity than reported elsewhere (39), the strains of *H. pylori* seen in infections in the West do not induce glandular atrophy or intestinal metaplasia (40). Additionally, a salty diet apparently may exacerbate the carcinogenetic activity of the bacterium (41).

Gastric cancer is different from adenocarcinoma of the EGJ (AEG classification) (3). Different patterns of lymphatic spread, which, in turn, might reflect different biological and carcinogenetic pathways, have been shown (1, 2, 42). Guggenheim and Shah, who reviewed the epidemiology of gastric cancer extensively, reported a great difference in the incidence of gastric cancer in developed countries—173,000 in males and 102,000 in females—compared to developing countries, in which the incidence is 467,000 and 247,000, respectively (43). In the United States, both the incidence and the mortality of gastric cancer have been continuously decreasing among all race groups except for whites, aged 25 to 39 years. In this group, they have been increasing since the 1970's (44). Some 70% of newly diagnosed gastric cancers occur in Eastern Asia, Central and Eastern Europe, and South America (45). However, in the Western world, both esophageal and gastric cancer are often first diagnosed in locally advanced tumor categories, as no upper gastrointestinal screening program currently exists (46).

Because Korea and Japan are the only countries with national guidelines or recommendations for upper GI screening and also provide mass screening nationwide, they detect upper GI cancer at earlier stages than do other countries and with correspondingly improved overall survival rates (47). Only 30% of patients who are clinically considered to have resectable disease and undergo surgery will have microscopically non-radical resections performed (48). Both the esophagus and the stomach are elastic organs with a lumen, and both rapidly compensate a partial or even a subtotal stenosis before the disorder becomes clinical apparent (49).

Embryology

The embryology of the vertebrate GI tract in mammalian development is considerably complex. The primitive alimentary canal is divided into the foregut (esophagus, stomach, duodenum, liver, gall bladder, pancreas, and spleen), the midgut (the intestine, including part of the duodenum, the small intestine, and the colon to the proximal two-thirds of the transverse colon) and the hindgut (from the distal third of the transverse colon to the rectum). During the first embryonic week the larynx, trachea, bronchus, and lungs appear as diverticula (50–53). The diverticula enlarges in length with a trough-like bulge of the foregut and later on the gut is separated from the trachea by the '*Septum esophago-tracheale*' on the day 36 of fetal growth (53).

The embryological process can be divided into three phases: the pre-embryonic (fertilization), the embryogenesis (from week 1 to 8), and the fetal (from week 9 to 20). Gastrulation, an early phase of embryonic developoment, refers to the period during which the trilaminar structure is organized into three germ layers: ectoderm, mesoderm, and endoderm (54). The primitive gut of the endoderm reveals the epithelium and the glands; connective tissue and muscles develop from the visceral mesoderm. During the fourth week of embryogenesis, the pharyngeal arches (*Arcus branchiales*) develop, serving as a morphological landmark for embryonic development and also as the analogue for multiple structures that develop later. Every pharyngeal arch consists of an artery, a vein, and a nerve, as well as a muscle and cartilaginous stick surrounded by mesenchyme.

This embryological history explains the fact that the different characteristics of lymphatic spread are related to the location of the cancerous tumor. The pharyngeal pouches and grooves form between the arches, separating them (55). The initial epithelium, which is single-layer and prismatic, changes by the fourth week into a two-layer epithelium. During the 2nd month, the rate of cell division increase so much, that the lumen is nearly or completely closed. This is the area of the tracheal bifurcation; if the luminal closure persists, an atresia appears; for that reason, an atresia is usually localized at the tracheal bifurcation (53). This change in the epithelium might be the reason for the difference between the lymphatic direction of the proximal esophagus and that of the distal. This indirect change in the epithelium seem reasonable serving as the explanation for the differing pattern of tumor spread according to the localization of the primary tumor.

Spence and Shroyer and Wells and Melton, in some detail, have reviewed the development of the endoderm; when totipotent cells from the epiblast (primitive ectoderm) derive, the ensuing process in embryogenesis is called gastrulation.

After differentiation, these cells "rearrange into three distinct germ layers: ectoderm, mesoderm and endoderm; the ectoderm forms skin and central nervous system, the mesoderm forms blood and muscle, and the endoderm forms the respiratory and digestive tracts (56, 57). After gastrulation, the endoderm in mice is one cell layer thick, comprises some 500 cells, which develop into the epithelium of the esophagus, lungs, stomach, intestine, many glands, and liver. The anterior gut tube gives rise to the thyroid and parathyroid glands, the thymus, the esophagus and the lungs, while the posterior gut tube gives rise to the small and large intestines.

During embryogenesis, transcription factors are suspected to "*... dictate cell fate through activation of specific target genes*." and furthermore, the process is thought to be based on a complex cell-cell communication (one factor and one gut cell-type) (57). In 1998, Swift, et al. showed that the formation of a multimeric complex between the PBX and MEIS subclasses of homeodomain proteins (HOX proteins) with the homeodomain protein, PDX1 (synonyms: IPF1, STF1, H1Hbox8, IDX1 or β-TGF1)—which itself is necessary for pancreogenesis—leads to a switch in its transcriptional activity, from an exocrine to an endocrine one (57, 58). Wells and Melton reviewed several *Hoxb* genes that are expressed by the anterior gut tube, as well as the deletion of the *shh*-responsive transcription factors *Gli2* and *Gli3*, which produced embryos lacking esophagus, trachea, or lungs (57).

These specific examples in embryology make evident, both for basic science and for specific cancer research, that searching for a single biomarker, or for a combination of some biomarkers, is unlikely to yield a situation that reflects reality in nature: the simple formation of one factor with different proteins into a multimeric complex can yield a biological effect entirely different from the original. Thus, the evidence embryology provides leads directly to these surgical, oncological, and interdisciplinary considerations:

- Esophageal squamous cell carcinoma are related to the embryogenesis of the trachea and to the pharyngeal loop and, therefore, to the left main bronchus. The majority of ESCC is located at and above the level of the tracheal bifurcation, but can be located at any point on the esophagus, whereas AC is mainly localized in the distal esophagus (6, 59).
- AC of the esophagus can be assigned to the umbilical loop, reflected by their main location in the distal esophagus and lymphatic spread the region of the celiac trunk (6, 59).
- Very often, bridges of connective tissue are situated between the esophagus and the trachea and the tracheal bifurcation and, here especially, to the left main bronchus. This may explain why ESCC tumors easily metastasize to the tracheal bifurcation and the left main bronchus (60–62). The localization at and above the tracheal bifurcation had been identified by Law, et al. as an independent risk factor for upper GI cancers (63).

Tumor growth

An unusual tumor growth, while rare, should be taken into account (64, 65), as otherwise, the diagnostic findings (e.g., an intramural tumor growth pattern) could be misinterpreted. This can be related to the fact that esophageal tumor tissue reaches the submucosal layers with an intraepithelial spread into a duct of the submucosal glands, which could lead, in its turn, to an intramural tumor growth. When such a growth is viewed by 18-FDG-uptake scan, it might be interpreted as a longitudinal esophageal uptake common in inflammatory esophageal reactions. Another rare phenomenon is a gastric spread from ESCC. Ebihara, et al. reported 13 intramural metastases to the stomach in a series of 1,200 esophageal squamous cell cancers (66). Therefore, an intramural growth of ESCC tissue that metastasizes to the stomach must be considered possible (66, 67). Gastric cancer spreads—despite lymhatic nodes—preferentially to the peritoneum, and, apparently, cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy may improve the dismal survival rates, between 2.2 and 8.8 months, in those cases for which a complete cytoreduction can be performed (68, 69).

Multimodal therapy

The factors that can affect patient outcome include complete macro- and microscopic tumor resection (R0-resection), the depth of tumor infiltration (T-category), the presence of lymph node metastasis (N-category), and the presence or absence of lymphatic vessel invasion (LVI) (1, 2, 60, 70, 71).

As the esophagus readily compensates for a partial obstruction of the lumen before getting symptomatic by dysphagia (60), the majority of patients with esophageal carcinoma at the time of diagnosis present with locally advanced tumors in which the option for a complete tumor resection is slight (1, 72). To increase the possibilities for radical resection, multimodal treatment strategies that increase local tumor control by increasing the proportion of R0-resections have been proposed and evaluated in clinical trials (73). They include neoadjuvant (pre-surgical) application of chemotherapy (CTx) and/or radiation therapy (RTx) and/or a combination of both (RTx/CTx) followed by surgical resection (71, 73–79). The impact of neoadjuvant treatment on overall survival seems to depend on whether a patient is a responder or a non-responder to the therapy applied (73). Preoperative CTx or RTx/CTx has been proposed as the standard treatment for patients with locally advanced esophageal carcinoma (80).

In 2006, it was proposed an altogether different perspective for cases in which some evidence exists that preoperative chemotherapy improves survival, but no evidence does that the overall rate of resections or the recurrence rate differs between the preoperative chemotherapy arm and that of surgery alone (81). These authors examined a total of 22 randomized trials and 4 meta analyses (82–107). They based their results of 2,097 patients on 12 randomized trials (83, 85, 86, 88, 91–93, 96, 99, 100, 101, 104), of which 8, with a total of 1,729 patients, revealed sufficient detail on patient survival to allow an evaluation (83, 85, 86, 88, 92, 93, 99, 101).

The current long-term survival data from Hong Kong (data collected between 2000 and 2004), in which randomly chosen patients with resectable ESCC by esophagectomy ($n = 45$) were compared to those who received definitive

RTx/CTX ($n = 36$): the 5-year survival rates were 29.4% and 50% respectively ($p = 0.147$) (108). The 5-year disease-free survival did not differ significantly between the two groups. The overall surgery-related postoperative compared to the RTx/CTx related morbidity was 38.6% and 67% respectively (p-value for comparison of treatment related morbidity was not provided).

The Dutch group working with the CROSS (Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study) group compared the survival of patients with resectable upper GI cancers who were randomly assigned to surgery alone or a regimen that combined RTx/CTX (carboplatin and paclitaxel with 41.4 gray [Gy]) and surgery: the median overall survival was 49.4 months in the multimodal treated arm and 24.0 months in the surgery arm ($p = 0.003$) (109). Survival data were calculated from the date of randomization, but the median time between randomization and surgery differed in the two groups. The average patient who had prior RTx/CTx waited more than 3 months (97 days) for surgery, while the patient that skipped pre-treatment waited an average 3 weeks (24 days). The group included different histology entities (75% AC and 23% ESCC) as well as different tumor locations (13% ad bifurcationem, 58% infrabifurcal, and between 22 and 26% within the EGJ). The postoperative morbidity rates, not reported in detail, were no greater in the group that had received preoperative treatment, nor was the rate of early mortality. A later, evidence-based review, classified as level 1 the evidence that preoperative chemotherapy offers a benefit for patients with locally advanced esophageal cancers; not clear was the benefit that induction chemotherapy might offer if given before a regimen of combined RTx/CTx (110).

The REAL3 randomized trial compared, in an equal number of cases of inoperable adenocarcinoma of the esophagus, the EGJ, and the stomach, the survival rate conferred by the regimen of epirubicin, oxaliplatin, and capectibabine (EOC-protocol) and the survival rate after the anti-EGFR antibody patitumumab was given in conjunction with that treatment; the authors concluded that the antibody conferred no benefit in survival rate (111). The EXPAND trial enrolled patients with advanced adenocarcinoma of the EGJ and of the stomach, randomly assigned to one group that received the anti-EGFR inhibitor cetuximab with capecitabine and cisplatin or to another, treated identically, but without the antibody (112). Neither trial revealed a benefit from adding one of the anti-EGFR inhibitors to a CTx regimen. However, an earlier paper reported an investigation of 1,346 patients with adenocarcinoma of the EGJ, in which the survival rates for AEG Type I were markedly better than those for the AEG Type II and III (1). If such criteria as tumor localization are less important for inclusion in a trial than other criteria, these make it difficult to judge a trial accurately. Additionally, others have reported that patients suffering from AEG Types II and III have a significantly higher prevalence of another prognostic factor, specifically diffuse-type carcinoma, as well as greater rates of lymph node metastasis and hepatic recurrence (113, 114).

The Japanese ACTS-GC trial investigated the outcomes of patients with curative resected (with D2-lymphadenectomy) locally advanced gastric adenocarcinoma. A randomly selected portion received posterior adjuvant chemotherapy with S-1, which was withheld from the control group. The 3-year survival rate in the adjuvant arm was 80.1%, compared to 70.1% in the group treated with surgery only (115). The ToGa trial investigated trastuzumab in Her2/neu-positive advanced adenocarcinoma of the stomach or the esophagogastrical junction; the 594 patients were randomly assigned trastuzumab plus chemotherapy ($n = 298$) or chemotherapy alone ($n = 296$): the patients in the trastuzumab arm showed an average 2-month survival benefit for the patients in the Trastuzumab arm (116). The CLASSIC trial, carried out in 37 centers of South Korea, China, and Taiwan, included 1035 patients with locally advanced adenocarcinoma of the stomach; after radical resection, including D2-lymphadenectomy, patients were randomly assigned to a group that received adjuvant chemotherapy with capecitabine and oxaliplatin or a group from which it was withheld: the 3-year disease-free survival of those in the surgery arm was 59%, compared to 74% of those that received chemotherapy after their surgery ($p < 0.0001$) (117).

Recently, 59,400 cases of upper GI cancers diagnosed in Germany between 1997 and 2006 have been compared to the SEER 13 database and analyzed extensively (118). In Germany, the overall age-standardized 5-year survival rate was 31.8% for stomach cancers and 18.3% for esophageal; for the U.S, the comparable rates were to 27.2% and 17.4%, respectively. These data are not equivalent to those reported recently from Japan, in which the 5-year survival rate for all cases of stomach cancer was near 60% (119). Lin, et al. showed, also, that the epidemiology of esophageal cancer within Asia differs significantly between Japan and China. They noted differences in cancer burden, incidence, mortality, and sex ratio, as well as risk factor profiles and genetics (120).

SUMMARY

The relevant criteria for evaluating and monitoring the response in clinical trials related to upper GI cancer include parameters to indicate states of tumor biology, histology, embryology, and tumor growth. The heterogeneity in the variables followed in these clinical trials is evident as carried out (81). In the trials they dissected, the study criteria might refer to histology or embryology, or not; to data points that depended on the type of chemotherapy, the type and dose of fractionated radiotherapy, the presence or absence of additional postoperative chemotherapy and the dosages thereof; and to the type of different surgical procedure, the length of the follow-up period, and the randomization—or lack of it—of the patients; also differences in the quality of the trials were noted (81). This heterogeneity can explain many of the discrepancies found in the peer-reviewed literature on the subject (6, 121) and it contributes to the difficulty in comparing the results of these trials.

The tumor itself is a hurdle. Of course, AC and ESCC differ sharply in their tumor biology (122, 123), the type of tumor growth they undergo (66), their involvement in

lymph nodes (1), the character of their invasion of lymphatic and vascular vessels (60, 124, 125), and their expression of genes (126–130) and proteins (125–130). However, in addition to the differences between AC and ESCC, the differences in the embryological development of their primary and metastatic sites—such as the heterogeneity of the tumor itself, of mutations, of mitochondrial DNA mutations, and of genetic variations—also contribute importantly to the picture (131–134). However, the actual understanding that mutations are the prime cause of the majority of cancers has recently been questioned, with an alternate proposal that describes a sequence of six consecutive events that could reasonably explain the origin of cancer (135).

A key to future discoveries in this area lies in both the availability and the utilization of big data in scientific endeavors. The big data tools may allow researcher to take advantage of an enormous variety of inclusion and exclusion criteria and thus manage the complex heterogeneity of the multiple molecular biological variables that make it so difficult to categorize humans to under just a few genetic profiles. The newly proposed anticancer strategy could open new directions in the exploration of the cancers and making progress in diagnosis and treatment of cancer (136).

We have shown how differences in the anatomy and embryology associated with histologically different upper GI tract tumors are translated both to different epidemiological findings and to discrepancies in tumor growth and tumor biology. Researchers designing future trials may take the reviewed variables into account when they determine their inclusion and exclusion criteria.

CONCLUSION

The findings in epidemiology, embryology, and molecular biology reported here highlight and demonstrate important considerations that investigators may should consider when designing their future research and clinical trials:

Epidemiological data demonstrate that acid reflux cannot be the sole reason for the increasing incidence of Barrett's cancer.

The primary reason for a distinct pattern of lymphatic spread according to the location of the primary tumor derives from embryology. Every pharyngeal arch consists of an artery, a vein, and a nerve, as well as a muscle and cartilaginous stick surrounded by mesenchyme, and the location of the tumor reveals its embryological origin. It is for this reason that the location of the primary tumor may be included as a significant variable when designing the inclusion criteria for a clinical trial.

The change in the epithelium during the fourth embryological week could be a key reason for the difference in the lymphatic direction of the proximal esophagus compared to the distal. The source of the cells in the two zones could indirectly be the reason for the different pattern of tumor spread according to the location of the primary tumor.

In one simple form of biomarker, a change of the protein produces a multimeric complex that leads to a completely novel biological effect, one completely different from that obtained before the change. Thus, searching for one biomarker or a combination them is unlikely to yield an outcome seen in nature. The statement applies equally to basic science and to specific cancer research.

On the base of evidence that is undoubtedly strong from a statistical point of view and which were derived from a good phase 3 study dataset, it may be of major help for the International Oncological community to reconsider different variables discussed in this paper, so that future studies include fewer differences and non-homogeneous disease categories.

DECLARATION OF INTEREST

The authors report no conflict of interest. The authors are responsible for the content and writing of this paper.

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Notice of Correction
Changes have been made to this article since its original online publication date of 24 September 2014.