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

Björn LDM Brücher,1−3 Masaki Kitajima,4 and Jörg Rüdiger Siewert5

Theodor-Billroth-Academy®, Munich, Germany; Richmond, VA, Sacramento, CA, USA,1 INCORE, International Consortium of Research Excellence of the Theodor-Billroth-Academy®, Munich, Germany; Richmond, VA, Sacramento, CA, USA,2 Bon Secours Cancer Institute, Richmond, VA, USA,3 International University of Health and Welfare, Tokyo, Japan,4 University of Freiburg, Freiburg, Germany5

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,
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).

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 mid-gut (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 development, 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, 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 B-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 lymphatic 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). Neoadjuvant 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
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]) 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 capecitabine (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 esophagogastric 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...
production of a multimeric complex that leads to a completely different pattern of tumor spread according to the location of the primary tumor.

According to the location of the primary tumor, the lymphatic direction of the proximal esophagus compared to the distal area could be the reason for the different patterns of tumor spread according to the location of the primary tumor.

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.

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.

REFERENCES

1. Siewert JR, Stein HJ, Feith M, Brücher BLD, Bartels H, Fink U. Histologic tumor type is an independent prognostic parameter in esophageal cancer: lessons learned from more than 1000 consecutive resections at a single centre in the western world. Ann Surg 2001;234(3):360–369.
2. Stein HJ, Feith M, Brücher BLD, Nährig J, Siewert JR. Early esophageal squamous cell and adenocarcinoma: Pattern of lymphatic spread and prognostic factors for long term survival after surgical resection. Ann Surg 2005;242(4):566–573.
3. Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophago gastric junction. Br J Surg 1998;85:1457–1459.
4. Lauren T. The two histological main types of gastric carcinoma (1965). Acta Pathol Microbiol Scand 64:31–49.
5. Halperin EC, Perez CA, Brady LW. Principles and Practice of Radiation Oncology, 5th edition. Perez and Brady's principles and practice of radiation oncology. Lippincott Williams & Wilkins, 2008.
6. Brücher BLD. Esophageal squamous cell carcinoma: preoperative combined radiochemotherapy from a surgical oncological viewpoint. Chirurg 2009;80:1011–1018.
7. Esophagus and esophagogastric junction. In: AJCC cancer staging manual, 7th edition Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti AI (eds.). Springer, 2010, 103–111.
8. Ectors N, Driessen A, de Hertog H, Gerin I, De Boever J. Is adenocarcinoma of the esophagogastric junction or cardia different from Barrett adenocarcinoma? Arch Pathol Lab Med 2005;128:183–185.
9. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, Cooper D, Gansler T, Lerro C, Fedewa S, Lin C, Leach C, Cannady RS, Cho H, Scoppa S, Hachey M, Kirch R, Jemal A, Ward E. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 2012;62:220–241.
10. Shikimic MB. Contrary to Nature. Washington, DC: U.S. Department of Health, Education and Welfare, 1977.
11. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, Feuer EJ, Thun MJ. Cancer statistics 2005. CA Cancer J Clin 2005;55:10–30.
12. Siegel, R, Nishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11–30.
13. Solaymani-Dodaran M, Card TR, West J. Cause-specific mortality of people with Barrett's Esophagus compared with the general population: a population-based Cohort study. Gastroenterology 2013;144:1375–1383.
14. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev 2010;19:1893–1907.
15. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008, Cancer incidence and mortality worldwide.
IARC CancerBase No. 10 [Internet]. Lyon (France): IARC, 2010. Available from: http://globocan.iarc.fr.

16. Website American Cancer Society: Survival rates for cancer of the esophagus by stage. 2014. http://www.cancer.org/cancer/esophagealcancer/detailedguide/esophagus-cancer-survival-rates

17. Nashimoto A, Akazawa K, Isobe Y, Miyashiro I, Kati H, Kodera Y, Tsujitani S, Seto Y, Furukawa H, Oda I, Ono H, Tanabe S, Kaminishi M. Gastric cancer treated in 2002 in Japan: 2009 annual report of the JGCA nationwide registry. Gastric Cancer 2013;16:1–27.

18. Songun I, Putter H, Kranenbarg EM, Sasaki M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010;11:439–449.

19. Blot WJ, McLaughlin JK. The changing epidemiology of esophageal cancer. Semin Oncol 1999;26:2–8.

20. Jemal A, Tiwari RC, Murray T, Ghafoor A, Samuels A, Ward E, Feuer EJ, Thun MJ. Cancer statistics, 2010. CA Cancer J Clin 2010;60:27–40.

21. Yang PC, Davis S. Incidence of cancer of the esophagus in the US 1991–2000. CA Cancer J Clin 2004;54:8–29.

22. Pohl H, Welch HG. The role of over-diagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst 2005;97:142–146.

23. Yang PC, Davis S. Incidence of cancer of the esophagus in the United States by histologic type. Cancer 1988;61:612–617.

24. Blot WJ, Devesa SS, Kneller RW. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA 1988;260:1287–1289.

25. Hesketh PJ, Clapp RW, Doos WG. The increasing frequency of adenocarcinoma of the esophagus by stage. 2004. CA Cancer J Clin 2004;54:8–29.

26. Lagergren J. Adenocarcinoma of oesophagus: what exactly is the size of the problem and who is at risk? Gut 2005;53:1070–1074.

27. Solaymani-Dodaran M, Logan RFA, West J, Card T, Coupland C. Gastric cancer: the epidemiology and the risk for gastroesophageal reflux disease and its complications. Ann Intern Med 2005;143:199–211.

28. El-Serag HB, Graham DY, Satia JA, Rabeneck L. Obesity is an independent risk factor for GERD symptoms and erosive esophagitis. Am J Gastroenterol 2005;100:1243–1250.

29. Ruffato A, Mattioli S, Perrone O, Lugaresi M, Di Simone MP, D’Errico A, Malvi D, Aprilie MR, Raulli G, Frassineti L. Esophagogastric metaplasia relates to nodal metastases in adenocarcinoma of esophagus and cardia. Ann Thorac Surg 2013;95:1147–1153.

30. Matsuhisa T, Aftab H. Observation of gastric mucosa in Bangladesh, the country with the lowest incidence of gastric cancer, and Japan, the country with the highest incidence. Helicobacter 2012;17:396–401.

31. Kubis S. Embryologie und Anatomie des Oesophagus. In Akutuelle Therapie des Oesophaguscarcims, Langhans, Schreiber, Haering, Reding, Siewert Buente (eds.). Berlin Heidelberg: Thieme Verlag Stuttgart 1985.

32. Kubik S. Embryologie und Anatomie des Oesophagus. In Akutuelle Therapie des Oesophaguscarcims, Langhans, Schreiber, Haering, Reding, Siewert Buente (eds.). Berlin Heidelberg: Springer Verlag, 1990.

33. O’Rahilly R, Müller F. Human Embryology & Teratology. 3rd edition. Chichester, Weinheim, Brisbane, Singapore, Toronto: Wiley-Liss New York 2001.

34. Kubik S. Embryologie und Anatomie des Oesophagus. In Akutuelle Therapie des Oesophaguscarcims, Langhans, Schreiber, Haering, Reding, Siewert Buente (eds.). Berlin Heidelberg: Springer Verlag, 1990.

35. Langmann J. Medizinische Embryologie. 7.Auflage. Georg Thieme Verlag Leipzig 1955.

36. Langmann J. Medizinische Embryologie. 7.Auflage. Georg Thieme Verlag Stuttgart 1985.

37. Kubik S. Embryologie und Anatomie des Oesophagus. In Akutuelle Therapie des Oesophaguscarcims, Langhans, Schreiber, Haering, Reding, Siewert Buente (eds.). Berlin Heidelberg: Springer Verlag, 1990.

38. O’Rahilly R, Müller F. Human Embryology & Teratology. 3rd edition. Chichester, Weinheim, Brisbane, Singapore, Toronto: Wiley-Liss New York 2001.

39. Graham A, Okabe M, Minami R. The role of the endoderm in the development and evolution of the pharyngeal arches. J Anat 2005;207:479–487.

40. Spencer JR, Lauf R, Shroyer NF. Vertebrate intestinal endoderm development. Dev Dyn 2001;220:501–520.

41. Wells JM, Melton DA. Vertebrate endoderm development. Annu Rev Cell Dev Biol 1999;15:393–410.

Copyright © 2014 Informa Healthcare USA, Inc.
58. Swift GH, Liu Y, Rose SD, Bischof LJ, Steelman S, Buchberg AM, Wright CV, MacDonald RJ. An endocrine-exocrine switch in the activity of the pancreatic homeodomain protein PDX1 through formation of a trimeric complex with PDX1b and MRG1 (MEIS2). Mol Cell Biol 1998;18:5109–5120.

59. Siewert JR, Feith M, Stein HJ. Esophagectomy as therapeutic principle for squamous cell esophageal cancer. Chirurg 2005;76:1033–1044.

60. Brücher BLDM, Siewert HJ, Wernern M, Siewert JR. Lymphatic vessel invasion is an independent prognostic factor in patients with a primary resected tumor with esophageal squamous cell carcinoma. Cancer 2001;92:2228–2233.

61. Liebermann-Meffert D. Anatomical basis for the extent and surgical approach to esophageal cancer. Dis Esoph 2001;14:81–87.

62. Liebermann-Meffert D, Stein HJ. Anatomy of the esophagus. In: Shackelford’s Surgery of the Alimentary Tract. 6th edition, J (eds.). WB Saunders, Philadelphia USA. 2005.

63. Law S, Wong KH, Kwok HM, Wong J. Predictive factors for postoperative pulmonary complications and mortality after esophagectomy for cancer. Ann Surg 2004;240:791–800.

64. McGregor DH, Mills G, Boudet RA. Intramural squamous cell carcinoma of the esophagus. Cancer 1976;37:1556–1561.

65. Von Rahden BHA, Brücher BLDM, Sarbia M. Esophageal Squamous Cell Carcinoma with entirely Intramural Growth Pattern. Virchows Archiv 2006;448:862–866.

66. Ebihara Y, Hosokawa M, Kondo S, Katoh H. Thirteen cases with intramural metastasis to the stomach in 1259 patients with oesophageal squamous cell carcinoma. Eur J Cardiothorac Surg 2004;26:1223–1225.

67. Koide N, Yazawa K, Koike S, Adachi W, Amano J, Ishii K. Two cases of gastric involvement of esophageal cancer: intramural metastasis and intramural lymph node metastasis. Hepatogastroenterology 1998;45:1619–1623.

68. Brücher BLDM, Piso P, Verwaal V, Esquivel J, Deraco M, Yone. mura Y, Gonzalez-Moreno S, Pez J, Königsrainer A, Ströhlein M, Levine EA, Morris D, Bartlett D, Glehen O, Garofalo A, Niss an A. Peritoneal carcinomatosis: overview and basics. Cancer Invest 2012;30:209–224.

69. Roviello F, Caruso S, Neri A, Marrelli D. Treatment and prevention of peritoneal carcinomatosis from gastric cancer by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: overview and rationale. Eur J Surg Oncol 2013;39:1309–1316.

70. Kelsen D. Preoperative chemoradiotherapy for esophageal cancer. J Clin Oncol 2001;19:283–285.

71. Brücher BLDM, Becker K, Lordick F, Fink U, Sarbia M, Stein H, Busch R, Zimmermann F, Molls M, Hölzer H, Siewert JR. The clinical impact of histopathologic response assessment by residual tumor cell quantification in esophageal squamous cell carcinomas. Cancer 2006;106:2119–2127.

72. Brücher BLDM, Wernern M, Sarbia M, Busch R, Dittler HJ, Molls M, Fink U, Siewert JR. Responders benefit from neoadjuvant radiochemotherapy in esophageal squamous cell carcinoma: results of a prospective phase-II trial. Eur J Surg Oncol 2004;30:963–971.

73. Urschel JD, Vasan H. A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer. Am J Surg 2003;185:538–543.

74. Malthaner RA, Wong RK, Rumble RB, Zuraw L. Members of the gastrointestinal cancer disease site group of cancer care ontario's program in evidence-based care: neoadjuvant or adjuvant therapy for resectable esophageal cancer: a systematic review and meta-analysis. BMC Med 2004;2:35.
comparison of evidence from meta-analyses of randomized trials and of historical control studies. Ann Oncol 1996;7:355–359.

91. Kok TC, van Lanschot J, Siersma PD, van Overhagen H, Tilanus HW. Neoadjuvant chemotherapy in operable esophageal squamous cell cancer: final report of a phase III multicenter randomized controlled trial. Proceedings of the Annual Meeting of the American Society of Clinical Oncology 1997;17:A984.

92. Law S, Fok M, Chow S, Chau KM, Wong J. Preoperative chemotherapy versus surgical therapy alone for squamous cell carcinoma of the esophagus: a prospective randomized trial. Thorac Cardiovasc Surg 1997;11:210–217.

93. Kelsen DP, Ginsberg R, Pajak TF, Sheahan DG, Gunderson L, Mortimer J, Estes N, Haller DG, Ajani J, Kocha W, Minsky BD, Roth JA. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 1998;339:1979–1984.

94. Kelsen DP, Winter KA, Gunderson LI, Mortimer J, Estes NC, Haller DG, Ajani JA, Kocha W, Minsky BD, Roth JA, Willett CG. Radiation Therapy Oncology Group; USA Intergroup. Long-Term Results of RTOG Trial 8911 [USA Intergroup 113]: a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer [Long-Term results of RTOG Trial 8911 [USA Intergroup 113]: a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer]. J Clin Oncol 2007;25:3719–3725.

95. Baba M, Natsugoe S, Shimada M, Nakano S, Shirao K, Kusano C, Fukumoto T, Aikou T. Does preoperative chemotherapy cause adverse effects on the perioperative course of patients undergoing esophagectomy for carcinoma? Jpn J Thoracic Cardiovasc Surg 1999;47:199–203.

96. Baba M, Natsugoe S, Shimada M, Nakano S, Kusano C, Fukumoto T, Aikou T, Akazawa K. Prospective evaluation of preoperative chemotherapy in resectable squamous cell carcinoma of the thoracic esophagus. Dis Esophagus 2000;13:136–41.

97. Fietkau R. No improvement of prognosis by neoadjuvant chemotherapy alone in operable esophageal carcinoma [Keine Verbesserung der Prognose des operablen Oesophaguskarzinoms durch eine alleinige neoadjuvante Chemotherapie]. Strahlentherapie und Onkologie 1999;175:251–252.

98. Clark P. Medical Research Council (MRC) randomized phase III trial of surgery with or without pre-operative chemotherapy in resectable cancer of the oesophagus. [Abstract] Br J Cancer 2000;83:A-CT2, 1.

99. Ancona E, Ruol A, Santi S, Merigliano S, Sileni VC, Koussis H, Zaninotto G, Bonavina L, Perachia A. Only pathologic complete response to neoadjuvant chemotherapy improves significantly the long term survival of patients with resectable esophageal squamous cell carcinoma: final report of a randomized, controlled trial of preoperative chemotherapy versus surgery alone. Cancer 2001;91:2165–2174.

100. Wang C, Ding T, Chang L. A randomized clinical study of preoperative chemotherapy for esophageal carcinoma. Zhonghua Zhong Liu Za Zhi 2001;23:254–255.

101. Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomized controlled trial. Lancet 2002;359:1727–1733.

102. Urschel JD, Vasan H, Blewett CJ. A meta-analysis of randomized controlled trials that compared neoadjuvant chemotherapy and surgery to surgery alone for resectable esophageal cancer. Am J Surg 2002;183:274–279.

103. Hohenberger W. Surgical resection with or without preoperative chemotherapy in esophageal cancer: a randomized controlled trial [German]. Strahlentherapie und Onkologie 2003;179:271–272.

104. Stiliadi I, Bokhyan V, Tryakin A, Suleymanov E, Kononets P, Malikhova O, Tjulandin S. Preoperative chemotherapy followed by resection vs. surgery alone for locally advanced esophageal carcinoma: interim analysis of a randomized study [Preoperative chemotherapy followed by resection vs. surgery alone for locally advanced esophageal carcinoma: interim analysis of a randomized study]. J Clin Oncol 2006;24:4055.

105. Thirion PG, Michiels S, Le Maître A, Tierney J. Individual patient data-based meta-analysis assessing pre-operative chemotherapy in resectable oesophageal carcinoma. J Clin Oncol 2007;25:4512.

106. Gębski V, Burmeister B, Smithers BM, Foo K, Zalcberg J, Sims J. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta analysis. Lancet Oncol 2007;8:226–234.

107. Boige V, Pignon J, Saint-Aubert B, Lasser P, Conroy T, Bouché O, Segol P, Bedenne L, Rougier P, Ychou M. Final results of a randomized trial comparing preoperative 5-fluouracil(F)/cisplatin (P) to surgery alone in adenocarcinoma of the stomach and lower esophagus (ASLE): FNLC ACCORD07–FFCD 9703 trial. J Clin Oncol 2007;25:4510.

108. Teoh AY, Chiu PW, Yeung WK, Liu SY, Wong SK, Ng EK. Long-term survival outcomes after definitive chemoradiation versus surgery in patients with resectable squamous carcinoma of the esophagus: results from a randomized controlled trial. Ann Oncol 2013;24:165–171.

109. van Hagen P, Hulshof MC, van Lanschot J, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaise JJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij RM, Reinders JG, Tilanus HW, van der Gaast A. CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer N Engl J Med 2012;366:2074–2084.

110. Shridhar R, Imani-Shikhabadi R, Davis B, Streeter OA, Thomas CR Jr. Curative treatment of esophageal cancer; an evidenced based review. J Gastrointest Cancer 2013;44:375–384.

111. Waddell T, Chau I, Cunningham D, Gonzalez D, Okines AF, Okines C, Wotherspoon A, Saffery C, Middleton G, Wadley J, Ferry D, Mansoor W, Crosby T, Coxon F, Smith D, Waters J, Iverson T, Falk S, Slater S, Peckitt C, Barbachano Y. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced esophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. Lancet Oncol 2013;14:481–489.

112. Lordick F, Kang YK, Chung HC, Salinan P, Oh SC, Bodoky G, Kurtova G, Volovat C, Mosayenemon Y, Gorbunova V, Park J0, Sawaki A, Celik I, Götte H, Melezinková H, Moehler M. Arbeitsgemeinschaft Internistische Onkologie and EXPAND Investigators: capcitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. Lancet Oncol 2013;14:490–499.

113. Ohno S, Tomisaki S, Iiwa H, Sakaguchi Y, Ichiyoshi Y, Maehara Y, Sugimachi K. Clinicopathologic characteristics and outcome of adenocarcinoma of the human gastric cardia in comparison with carcinoma of other regions of the stomach. J Am Coll Surg 1995;180:577–582.

114. Yuasa N, Miyake H, Yamada T, Ebata T, Nimura Y, Hattori T. Clinicopathologic comparison of Siewert type II and III adenocarcinoma of the gastroesophageal junction. World J Surg 2006;30:364–371.

115. Sakuramoto S, Sasaki M, Yamaguchi T, Kinoshita T, Fujii M, Nakashima A, Furukawa H, Nakajima T, Ohashi Y, Iamamura H, Higashino M, Yamamura Y, Kuriya A, Arai K. ACTS-GC Group. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007;357:1810–1820.

116. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulisok E, Hill J, Lehnle M, Rüschoff J, Kang YK (2010) ToGa Trial...
Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687–697. Erratum in: Lancet 2010;376:1302.

117. Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, Lee KW, Kim YH, Noh SI, Cho JY, Mok VJ, Kim YH, Ji J, Yeh TS, Button P, Sirzén F, Noh SH. CLASSIC trial investigators. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012;379:315–321.

118. Hiripi E, Jansen L, Gondos A, Emrich K, Holleczek B, Katalinic A, Luttmann S, Nennecke A, Brenner H, Gekid Cancer Survival Working Group. Survival of stomach and esophageal cancer patients in Germany in the early 21st century. Acta Oncol 2012;51:906–914.

119. Ito Y, Nakayama T, Miyashiro I, Ioka A, Tsukuma H. Conditional survival for longer-term survivors from 2000–2004 using population-based cancer registry data in Osaka, Japan. BMC Cancer 2013;13:304.

120. Lin Y, Totsuka Y, He Y, Kikuchi S, Qiao Y, Ueda J, Wei W, Inoue Ito Y, Nakayama T, Miyashiro I, Ioka A, Tsukuma H. Epidemiology of esophageal cancer in Japan and China. J Epidemiol 2013;23:233–242.

121. Brücher B, Schuhmacher C, Feith M, Stein H. Barrett’s esophagus: treatments of adenocarcinoma I. Ann N Y Acad Sci 2011;1232:248–264.

122. Brücher B, Schuhmacher C, Feith M, Stein H. Barrett’s esophagus: treatments of adenocarcinoma II. Ann N Y Acad Sci 2011;1232:265–291.

123. Twaddell WS, Wu PC, Verhage RJ, Feith M, Ilson DH, Schuhmacher CP, Luketich JD, Brücher B, Vallbohmer D, Hofstetter WL, Krasna MJ, Kandilor D, Schneider PM, Wijnhoven BP, Sontag SJ. Barrett’s esophagus: treatments of adenocarcinoma I. Ann N Y Acad Sci 2011;1232:248–264.

124. Von Rahden BH, Stein HJ, Feith M, Becker K, Siewert JR. Lymphatic vessel invasion as a prognostic factor in patients with primary resected adenocarcinomas of the esophagogastric junction. J Clin Oncol 2005;23:874–879.

125. Möbius C, Freire, Becker I, Feith M, Brücher BL, Hennig M, Siewert JR, Stein HJ. VEGF-C expression in squamous cell carcinoma and adenocarcinoma of the esophagus. World J Surg 2007;31:1768–1772.

126. Kitagawa Y, Ueda M, Ando N, Ozawa S, Shimizu N, Kitajima M. Further evidence for prognostic significance of epidermal growth factor receptor gene amplification in patients with esophageal squamous cell carcinoma. Clin Cancer Res 1996;2:909–914.

127. Sarbia M, Pühringer-Oppermann F, Brücher B. Predictive value of molecular markers (p53, EGFR, ATM, CHK2) in multimodal treated esophageal squamous cell carcinoma. Br J Cancer 2007;97:1404–1408.

128. Brücher B, Keller G, Werner M, Müller U, Lassmann S, Cabras A, Fend F, Busch R, Stein H, Allescher HD, Molls M, Siewert JR, Höfler H, Specht K. Using Q-RT-PCR to measure cyclin D1, TS, TP, DPD, and Her-2/neu as predictors for response, survival, and recurrence in patients with esophageal squamous cell carcinoma following radiochemotherapy. Int J Colorectal Dis 2009;24:69–77.

129. Mathe EA, Ngyen GH, Bowman ED, Zhao Y, Budhu A, Schetter AJ, Braun R, Reimers M, Kumamoto K, Hughes D, Altorki NK, Casson AG, Liu CG, Wang XW, Yamaihara N, Hagiwara N, Dannenberg AJ, Miyashita M, Croce CM, Harris CC. MicroRNA expression in squamous cell carcinoma and adenocarcinoma of the esophagus: associations with survival. Clin Cancer Res 2009;15:6192–6200.

130. Bandla S, Pennathur A, Luketich JD, Beer DG, Lin L, Bass AJ, Godfrey TE, Little VR. Comparative genomics of esophageal adenocarcinoma and squamous cell carcinoma. Ann Thorac Surg 2012;93:1101–1106.

131. Zhou J, Zhao LQ, Xiong MM, Wang XQ, Yang GR, Qiu ZL, Wu M, Liu ZH. Gene expression profiles at different stages of human esophageal squamous cell carcinoma. World J Gastroenterol 2003;9:9–15.

132. Ziogas DE, Roukos DH. Limitations of isolated tumor cells in gastric cancer: heterogeneity requests systems biology approaches towards personalized medicine. Ann Surg Oncol 2010;17:343–344.

133. He Y, Wu J, Dressman DC, Iacobuzio-Donahue C, Markowitz SD, Velculescu VE, Diaz LA Jr, Kinzler KW, Vogelstein B, Papadopoulos N. Heteroplasmic mitochondrial DNA mutations in normal and tumor cells. Nature 2010;464:610–614.

134. Longo DL. Tumor heterogeneity and personalized medicine. N Engl J Med 2012;366:956–957.

135. Brücher B, Jamall IS. Epistemology of the origin of cancer: a new paradigm. BMC Cancer 2014;14:331.

136. Brücher B, Lyman G, van Hillegersberg R, Pollack RE, Lordick F, Yang HK, Ushijima T, Yeoh KG, Skricka T, Polkowski W, Wallner G, Verwaal V, Garofalo A, D’Ugo D, Rivello F, Steinau HU, Wallace TJ, Daumer M, Maiblile N, Reid III TJ, Ducruex M, Kitagawa Y, Knuth A, Zilberman B, Steele SR, Jamall IS. Imagine a world without cancer. BMC Cancer 2014;14:186.

**Notice of Correction**

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