### Editorial

### Personalized and targeted therapy for esophageal squamous cell carcinoma

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Abbreviation: ESCC, esophageal squamous cell carcinoma; NGS, next-generation sequencing; OS, overall survival; WES, whole exome sequencing; WGS, whole genome sequencing

Esophageal cancer is the eighth most prevalent cancer in the world. Each year there are more than 480,000 incipient cases and 400,000 deaths with more than 80% occurring in developing countries [1]. Esophageal squamous cell carcinoma (ESCC) is the predominant histologic type worldwide. In China alone, more than 280,000 new cases and 200,000 deaths were estimated in 2010 [2]. Despite the many advances in diagnosis and treatment in past decades, the 5-year survival rate for patients with esophageal cancer ranges from 15-20% [3]. This is mainly due to late diagnosis, aggressiveness of the cancer, and lack of effective treatment strategies [4].

Surgery remains the mainstay of treatment for ESCC although surgery alone achieves poor locoregional control and poor long-term outcome. The 5-year survival rate for non-metastatic ESCC is 10~40% if treated with surgery alone [5]. Unfortunately, esophagectomy itself is a complex procedure with significant morbidity and mortality, as 2~25% patients die within 30 days after surgery [5].

Since 40%~50% surgical cases have stage III disease [4, 6, 7], most patients are given neoadjuvant chemotherapy with cisplatin/fluorouracil and carboplatin/paclitaxel. A recent meta-analysis showed a significant improvement in overall survival (OS) after neoadjuvant chemotherapy, with a 13% reduction of relative mortality risk and a 5.1% increase of 2-year survival. However, this difference was not statistically significant [7].

At the time of diagnosis, more than 50% of the patients were present with an unresectable or metastatic form of ESCC[4]. Chemoradiotherapy is preferred as a non-surgical approach if there are no contraindications. This combination approach yields better palliative outcomes than radiotherapy alone and improves long-term progression-free survival [8], although its efficacy in locoregional control is inferior to surgery [9]. For chemotherapy, fluorouracil and cisplatin with or without a third drug (such as epirubicin, taxane) is known as the most efficacious combination [10].

Approximately 40% of patients for whom first-line treatment fails will be potential candidates for second-line therapy [11]. Unfortunately, salvage choices of second-line therapy are sparse, and there is no consensus on the optimum [10]. Survival of these patients is poor with a median OS of 5-10 months [12-22]. This data points to a great need of further understanding the mechanisms of ESCC and developing novel and effective approaches for early diagnosis, prevention and therapy.

Recently, tremendous progress has been made in cancer genomics and epigenomics with the advent of high-throughput techniques like next-generation sequencing (NGS). Three groups have reported the genetic landscape of human ESCC with whole genome sequencing (WGS) and whole exome sequencing (WES) [23-25]. Genomic alterations include: (1) Single nucleotide variants of many genes with a relatively significant frequency (≥5%), such as p53, KMT2D, Notch1/2/3, FAT1/3, Syne1, EP300, Rb1, Nfe2l2, Cdkn2a, Ajuba, Crebbp, Kdm6A, Fbxw7, MLL2/3, Pik3ca, Pten, Arid2, Pbrm1, etc; (2) Copy number alterations of many genes with a relatively significant frequency (≥5%), such as CCND1, FGFs, CDKN2A, CDKN2B, Pik3ca, Dvl3, LRP5/6, KRas/MRas, EGFR, Akt1, Bcl2l1, Notch1/2/3, E2F1, SFRP4, SOS1/2, Birc5, Yap1, Sox2, Myc, IL7R, etc; (3) Alterations in multiple signaling pathways such as cell cycle regulation, apoptosis regulation, DNA damage control, RTK-Ras-MAPK-PI3K-Akt pathway, Hippo pathway, Notch pathway, Wnt pathway, Nfe2l2/Keap1 pathway, histone modifications, etc. The overall mutation pattern appears similar to that of head & neck SCC [26, 27], but different from that of esophageal adenocarcinoma [28, 29] and lung SCC [30].

In addition to these descriptive data, smoking was found to be not related with signature mutations [23], but the lack of alcohol consumption was associated with a cluster of gene mutations [25]. Viral integration was not found in the genomes of 88 subjects [25]. Trinucleotide signature analysis suggested DNA cytidine deaminase (APOBEC3B) induced deamination was mainly responsible for mutations [31] [24]. Moreover, mutations of single genes or gene clusters were associated with patient survival, for example, EP300 mutation [23, 25]. Certain genes, for example, XPO1, were explored as a therapeutic target [24].

These landmark studies provided the research community an enormous amount of information to better understand the molecular mechanisms of ESCC. This Editorial is aimed to gain insights from such studies, and propose personalized and targeted therapy as a research direction in the future.

1. **Interpretation of Genomics Data**

**Driver genes and driver mutations** Currently available bioinformatics tools have been designed to prioritize gene mutations at the nucleotide level, gene level, pathway level, and network level.The number of non-synonymous somatic mutations per ESCC averaged more than 80. If a solid tumor ordinarily requires 5 to 8 hits (not necessarily 5-8 mutations) as suggested by classical epidemiologic studies, most of these mutations should be “passengers” instead of “drivers” which can offer selective growth advantage to the tumor cell [32]. Therefore it is critical to identify which gene mutations are cancer drivers.

Since driver mutations may occur at high or low frequencies [33], it may not be safe to prioritize driver mutations according to their frequencies. However, as a clinically relevant parameter, a high frequency of a mutation does support its potential significance in carcinogenesis. Other than Mut-drivers (mutated drivers), Epi-driver is a class of driver genes that are not frequently mutated but aberrantly expressed in tumors through epigenetic alterations in DNA methylation or chromatin modification. Although epigenetics in ESCC has been studied for many years [34, 35], it is still not clear how to differentiate epigenetic alterations that bring forth a selective growth advantage from those that do not [32]. According to Vogelstein’s 20/20 rule, only 125 ‘Mut-driver’ genes of human cancers have been discovered to date, and the number is nearing saturation [32]. Tamborero *et al* reported a list of 291 high-confidence cancer driver genes and 144 candidate genes from 12 different types of cancer [36]. Several databases have become available. For example, Network of Cancer Genes (NCG 4.0) contains 537 experimentally supported genes and 1463 candidate genes inferred using statistical methods [37]. Candidate Cancer Gene Database contains cancer driver genes from forward genetic screens in mice [38]. Considering tissue specificity of ESCC, there is a need of compiling a cancer driver gene list to support future research on ESCC therapy. However, it should be pointed out that cancer driver genes may contain both driver mutations and passenger mutations in cancer. For example, Apc mutations truncating the N-terminal amino acids are driver mutations, while those affecting other regions are passenger mutations. Even for the same driver gene (e.g., K-Ras), different driver mutations (e.g., mutations at codon 12, 13 and 61) have different impact on carcinogenesis and clinical behaviors [39-41]. Because of these complexities, efforts need to be made in order to identify personalized driver genes in cancer [42].

**Pathways and network** Increasing evidence suggests that dysregulation of cellular signaling pathways, rather than individual mutations, contributes to ESCC [43-45]. Driver genes usually do not work in isolation, but together to alter cellular processes [46]. There is a growing consensus that pathways rather than single genes are the primary target of mutations [47]. It is interesting that mutations in various components of a single pathway tend to be mutually exclusive [48]. Once driver genes or driver mutations are identified, the next step is to focus on driver pathways with genes grouped together according to the biochemical pathways that they play functional roles in. Pathway activity may be further validated by the downstream readouts, e.g., mRNA and protein expression, morphology, function. Incorporation of immunohistochemistry data or even proteomics data may help evaluation of the pathway activity [49, 50].

One major challenge in analyzing genomics data of ESCC is the lack of information of esophagus-specific pathways. Pathway databases, e.g., KEGG, are fairly incomplete and lack tissue and cell specificities. Applying such pathway information in analyzing ESCC data may generate misleading outcome. For example, using ChIP-seq analyses, Sox2-regulated genes in ESCC cells are different from those in embryonic stem cells because in ESCC Sox2 tends to interact with p63 as opposed to Oct4 in embryonic stem cells [51]. Identifying bona fide target genes and using expression profile of these genes to infer pathway activity in ESCC will be critical in the future [52].

Very few bioinformatics methods involve a principled procedure for taking account of pathway interactions, *i.e.,* pathways that are mutated in the same sample, and that are mutated together across a large subset of samples [24]. Similar to expression-based stratification, network-based stratification of tumor mutations can identify cancer subtypes to guide treatment and prognosis [53]. Categorizing ESCC into multiple subtypes according to its molecular alterations may be a practical step leading to final personalization of ESCC therapy. In fact, subtyping has been shown to be a successful approach in managing other cancers [54].

**Drug selection** Selecting drugs according to genomics data has led to promising results in early studies on personalized and targeted therapy [55]. So far, most clinically approved targeted drugs are directed against kinases. Some of these have been tried for ESCC (Table 1). Gefitinib, an EGFR inhibitor, has been tested as a second-line treatment for esophageal cancer. In unselected patients it does not improve OS, but has palliative benefits in a subgroup of difficult-to-treat patients with short-life expectancy [56]. Unfortunately, only a few cancer drivers have enzymatic activities which are targetable in this fashion, and whether a target is druggable becomes a research question [57]. Once a drug target is verified, drugs or experimental compounds may be developed. Several databases are available for search, e.g., Therapeutic Target Database [58], DrugBank 4.0 [59].

If the target is not druggable, its regulatory proteins or functional pathway may be targeted. For example, cyclin D1 amplification is commonly seen in human ESCC. Since cyclin D1 mainly functions through CDK activation, CDK4 and CDK6 can be targeted instead of cyclin D1 [60]. P53 is the most commonly mutated genes in human ESCC. Instead of targeting p53, many strategies have been tested to restore the functions of p53 by delivering wild-type p53, targeting MDM2-p53 interaction, restoring the functions of mutant p53, targeting p53 family proteins, or eliminating mutation p53 [61, 62].

In addition to selecting drugs for targeted therapy, analysis of drug-metabolism genes in germ-line DNA can also optimize dosing and identify drug toxicity risk [63, 64]. With the help of a database, e.g., Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB), genetic variations can be associated with drug response [65].

1. **Issues in Targeted Therapy**

**Cancer heterogeneity** Various combinations of drivers and pathways result in intratumoral, intermetastatic, intrametastatic or interpatient heterogeneities. It may explain why the same treatment brings about favorable response or resistance in different patients, and why a patient responds well initially and develops resistance over time. Intratumoral heterogeneity has been validated using single-cell RNA-seq of primary glioblastoma [66]. Since the majority of cancer gene mutations do appear in multiple regions of the same tumor, single-region sequencing may be adequate to identify the majority of cancer gene mutations [67]. It can be predicted that most cancer cells in the same tumor may share the major alterations. If this is proven true in ESCC, it will make treatment more predictable.

Intermetastatic and intrametastatic heterogeneity may not be a big concern. Despite many years of research, we have failed to identify a group of so-called metastasis genes. Metastasis is probably stochastic depending on the environment in the metastatic site [68]. Therefore if we can understand genetic and epigenetic alterations in the primary tumor well, all cancer cells left at the primary site or metastatic sites are expected to behave in the same way. Nevertheless, the prevalence of different patterns of tumor heterogeneity needs to be more robustly assessed in large patient cohorts, and new patterns will probably be identified as the wealth of genomic data of ESCC is analyzed [69].

**Drug resistance** If carcinogenesis is regard as an evolutionary process with successive new mutations driven by Darwinian selection, chemotherapy, radiotherapy and target therapy may all provide a potent source of artificial selection to alter clonal dynamics. Consequently, the anti-tumor therapy may lead to resistance [70]. Indeed, targeted therapy is associated with a high rate of resistance at the very beginning when Vermurafeni, a BRAFV600E inhibitor, was clinically used for melanoma. Combination of a BRAFV600E inhibitor (dabrafenib) and a MEK inhibitor (trametinib) resulted in better response, yet did not prevent resistance from occurring. Distinct mechanisms include mutations in the target, reactivation of the targeted pathway, hyperactivation of alternative pathways, and cross-talk with the microenvironment [71]. Resistant cells may undergo a process called phenotype switching under the selection of targeted therapy [72]. Understanding these mechanisms has led to additional efforts in finding new therapy targeting the same target, the same pathway, or alternative pathways [73-75].

Three strategies are feasible measures in handling drug resistance. Before treatment, both bioinformatics and experimental modelling may inform heterogeneity [76-78]. There is a need to develop clinically useful measures of heterogeneity [79]. Secondly, during treatment, limited success can be achieved with a single agent. The combination strategy may be the best way to refrain from the inevitable development of resistance to single-drug targeted therapies [47]. Thirdly, longitudinal tumor sampling will be essential to decipher the impact of tumor heterogeneity on cancer evolution, and developing minimally invasive methods to profile heterogeneous tumor genomes will play a major part in following clonal dynamics in real time [77]. For ESCC, repeated biopsy, circulating tumor DNA analysis [80, 81], and exfoliative cells [82, 83] are all valid options for this purpose.

**Exceptional responders** As opposed to drug resistance, exceptional responders are patients who have a unique response to treatments that are not effective for most other patients. NCI has embarked on the Exceptional Responders Initiative to understand the molecular underpinnings of exceptional responses to treatment in cancer patients. In the past, exceptional responders led to clinical breakthrough in treatment of certain type of cancer, and understanding of novel molecular mechanisms of carcinogenesis [84]. It is foreseeable that careful characterization and follow-up of these exceptional responders will be of great value in the future practice of personalized and targeted therapy of ESCC

**Side effects**  As compared with traditional chemotherapy, targeted therapy is better tolerated. However, it does produce toxicities based on several major mechanisms, for example, on-target toxicity, off-target toxicity, hypersensitivity-related toxicities, metabolite-induced toxicities. VEGFR inhibitors cause hypertension and EGFR inhibitors cause toxicities in tissues where EGFR normally play an important functional role in tissue maintenance (e.g., skin, gastrointestinal epithelia). Some of these on-target toxicities may serve as surrogate biomarkers for clinical response [85-89]. Considering these potential side effects, clinical oncologists should be prepared to educate the patients and undertake respective preventive and therapeutic measures.

1. **Research Approaches for Targeted Therapy**

For genomics-guided research, cell line-based platforms have become an indispensable tool [90, 91]. Clarification of genetic and epigenetic alterations of established ESCC cell lines would be great tools for preclinical drug development [92, 93], in particular, KYSE series of ESCC cell lines which have been sequenced [23-25]. Patient-derived ESCC cells can be used for selection of potential individualized therapy [94, 95]. These cells are particularly useful in identifying effective drug combinations for acquired resistance [96].

Several models have been put into preclinical research and even clinical applications. A patient-derived xenograft model of ESCC is created when cancerous tissue from a patient’s primary tumor is implanted directly into immunodeficient mice. This model provides solutions to the translational challenges that researchers and clinicians face in cancer drug research and selection [97, 98]. Carcinogen-induced models, for example, the N-nitrosomethylbenzylamine-induced model, are a classical model for ESCC research. It mimics human ESCC in not only etiology and histopathology, but also in molecular alterations (e.g., p53 mutations [99, 100]). However, exactly how well this model can mimic human ESCC at the genomics level has not been well studied. WES has already shown that carcinogen-induced and genetically engineered models lead to carcinogenesis through different routes. A carcinogen-induced model is particularly important in understanding the complex mutation spectra seen in human cancers [101]. It is encouraging that genomic alterations in 4-nitroquinoline 1-oxide-induced mouse tongue cancer are well preserved [100].

Genetically engineered mouse models of human cancers have proven essential to dissect the molecular mechanisms behind carcinogenesis [102], and provide robust preclinical platforms for investigating drug efficacy [103] and resistance [104-106]. Using Sox2, an amplified oncogene in ESCC [107], as an example, transgenic Sox2 overexpression drives the complete process of carcinogenesis in mice [108]. This model can readily be used for preclinical drug development for Sox2-overexpressing ESCC. Although it may be difficult to target Sox2 itself, its downstream genes or pathways, e.g., Akt/mTOR pathway, can be targeted [95]. Biochemical outcomes may be used for assessment of the efficacy of a Sox2-targeting therapy even when it does not reduce tumor incidence or size in mice. Genome engineering with CRISPR-Cas9 *in vivo* is an extremely promising technique in identifying cancer driver genes and testing drug targets [109]. It may ultimately be used for human gene therapy in the future [110].

As a hallmark of human cancer and a crucial determinant of variable response to treatment [91], genomic heterogeneity calls for revision of clinical trial design currently in use in order to implement personalized therapy [111]. The majority of traditional prospective clinical trials are disease-based or histopathology-based. Genomics-driven trials, for example, mutation-based trial, pathway-based trial, subtype-based trial, will be more widely used in drug development [112]. Two genomics-based study designs are currently being utilized to develop targeted therapies, exploratory design and multi-agent sequential design [113]. ESCC fits both study designs very well because the esophagus can be biopsied before and after treatment.

1. **Future Perspectives**

The biggest challenge in ESCC treatment is the translation from genomic discoveries into personalized therapies based on strategies sketched from patients’ individual profiles [111]. The evasiveness of cancer cells has been a frustrating observation of clinical oncologists. Vogelstein *et al* proposed that “there is order in cancer” [32] ,pointing to the need to tackling ESCC as a disease status with its own homeostatic mechanisms. From the perspective of ten hallmarks of human cancer [114], Hanahan proposed three strategically distinct “battlespace-guided plans” for cancer treatment, disruption of the enemy’s many capabilities, defense against cancer’s armed forces, and integration of the geographies of the battlefields [115]. It is clear that combination therapy targeting multiple mechanisms would be the only option in the future. Using immunotherapy as an example, tremelimumab (anti-CTLA4) has been tested as a second-line therapy for esophageal cancer. Although the clinical response was not impressive, its biological effect on T cell activation seemed to be associated with clinical response [116]. Recent development of immunotherapy based on Erbb2IP mutation-specific CD4+ T cells [117] and PD-L1 suppression is also quite promising. For patients in which pre-existing immunity is suppressed by PD-L1, blocking PD-L1 enhanced anti-cancer immunity including one case of esophageal cancer [118]. A realistic option in the near future can be a combination of target drugs and traditional chemoradiotherapy for ESCC. Target drugs are expected to kill cancer cells with specific genomic alterations, while traditional therapy acts in a much broader manner.

Technical issues of NGS and bioinformatics are still big hurdles and prevent us from gaining full insights into the mechanisms of carcinogenesis and metastasis of ESCC. WGS nonetheless correlates with incomplete coverage of inherited disease genes, low reproducibility of genetic variation with the highest potential clinical effects, and uncertainty about clinically reportable WGS findings [119]. WES is particularly prone to errors as only 61% of the mutated genes in ESCC are transcribed [24]. This is similar to what has been observed in pancreatic cancer: only 63% of the expected 251 driver gene mutations were identified, suggesting a 37% false negative rate. Marked discrepancies in the detection of missense mutations in identical cell lines (57.38%) have been reported due to inadequate sequencing of GC-rich areas of the exome [120]. The protein-coding genes account for only ~1.5% of the total genome. Although the vast majority of the alterations in noncoding regions are presumably passengers, some of these may be drivers, for example, mutations in Tert promoter [121, 122].

New computational and bioinformatics tools still need to be developed and improved due to low concordance of multiple variant-calling pipelines [123] [124]. Directly comparing genome sequence reads may improve data quality as compared with initial alignment of reads to a reference genome [125].

Apart from the logistic challenges, financial, social and ethical challenges are also posed by personalized and targeted therapy [55]. In addition to viewing a patient’s cancer as a biological phenomenon waiting for medical attention alone, personalized therapy emphasizes biopsychosocial care by including communication and information giving, psychological and emotional well-being, enhancing function, addressing financial and spiritual concerns, symptom control, and social support [126]. If we look at one specific patient’s ESCC from all these perspectives, a tumor board should involve not only medical staff but also supporting staff (Figure 1).

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| Table 1. Clinical trials on targeted therapy of ESCC \*   |  |  |  | | --- | --- | --- | | Target | Agent | NCT Number (Phase) | | EGFR | Erlotinib | NCT00045526 (II), NCT00030498 (I), NCT00397384 (I), NCT00524121 (II), NCT01013831 (I), NCT01561014 (I), NCT01752205 (III) | | Gefitinib | NCT00093652 (I/II), NCT00258297 (II), NCT00258323 (II), NCT00268346 (II), NCT00290719 (I) | | Icotinib | NCT01973725 (II) | | Lapatinib | NCT00239200 (II), NCT01666431 (II) | | Nimotuzumab | NCT02272699 (II/III), NCT01232374 (II), NCT01336049 (II), NCT01402180 (II/III), NCT01486992 (II), NCT01688700 (II), NCT01993784 (I/II), NCT02011594 (II), NCT02034968 (II), NCT02041819 (II) | | Panitumumab | NCT01077999 (II), NCT01262183 (II), NCT01627379 (III) | | PF00299804 | NCT01608022 (II) | | Cetuximab | NCT02123381 (II), NCT00109850 (II), NCT00165490 (II), NCT00381706 (II), NCT00397384 (I), NCT00397904 (II), NCT00425425 (I/II), NCT00445861 (I/II), NCT00509561 (II/III), NCT00544362 (I/II), NCT00655876 (III), NCT00757549 (0), NCT00815308 (II), NCT01034189 (II), NCT01107639 (III) | | IGF1R | Cixutumumab | NCT01142388 (II) | | PI3K | BKM120 | NCT01626209 (I), NCT01806649 (II) | | BYL719 | NCT01822613 (I/II) | | Rigosertib | NCT01807546 (II) | | HDAC | Entinostat | NCT00020579 (I) | | Vorinostat | NCT00537121 (I), NCT01249443 (I) | | HER3 | LJM716 | NCT01598077 (I), NCT01822613 (I/II) | | VEGFR | Vandetanib | NCT00732745 (I) | | Sorafenib | NCT00917462 (II) | | VEGFA | Bevacizumab | NCT01212822 (II) | | PD-L1 | MEDI4736 | NCT01938612 (I) | | Bcl-2 mRNA | Oblimersen | NCT00003103 (I/II) | | CDK9 | Alvocidib | NCT00006245 (II) | | CRM1 | Selinexor | NCT02213133 (II) | | FGFR | AZD4547 | NCT01795768 (II) | | KIF11 | Litronesib | NCT01059643 (II) | | TACSTD2 | IMMU-132 | NCT01631552 (I/II) | |  |  |  |  |  |  |  |  |  |

\* “Esophageal squamous cell carcinoma” was searched at the website ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)). Targeted therapy has been or is being tried in 62 of 204 studies. Some of these agents target multiple molecules, for example, Lapatinib (EGFR and Erbb2), Rigosertib (PI3K and PLK), Vandetanib (VEGFR, EGFR and RET), Sorafenib (VEGFR, PDGFR and RAF).

Figure legend:

Figure 1. Personalized and targeted therapy for ESCC. The strategy is based on the concept that a patient’s genetic makeup should guide his or her treatment. After a series of molecular analyses on tumor samples, bioinformatics is expected to identify driver genes, pathways, cancer subtype, and target drugs. A tumor board will synthesize all information and generate a personalized treatment plan. Non-responders may be analyzed in a similar manner during subsequent surveillance and further treated.

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