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REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

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Recent Advances From Basic and Clinical Studies of Esophageal Squamous Cell Carcinoma

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Esophageal squamous cell carcinoma (ESCC) is one of the most aggressive squamous cell carcinomas and is highly prevalent in Asia. Alcohol and its metabolite, acetaldehyde, are considered definite carcinogens for the esophagus. Polymorphisms in the aldehyde dehydrogenase 2 gene, which encodes an enzyme that eliminates acetaldehyde, have been associated with esophageal carcinogenesis. Studies of the mutagenic and carcinogenic effects of acetaldehyde support this observation. Several recent large-scale comprehensive analyses of the genomic alterations in ESCC have shown a high frequency of mutations in genes such as *TP53* and others that regulate the cell cycle or cell differentiation. Moreover, whole genome and whole exome sequencing studies have frequently detected somatic mutations, such as G:C→A:T transitions or G:C→C:G transversions, in ESCC tissues. Genomic instability, caused by abnormalities in the Fanconi anemia DNA repair pathway, is also considered a pathogenic mechanism of ESCC. Advances in diagnostic techniques such as magnifying endoscopy with narrow band imaging or positron emission tomography have increased the accuracy of diagnosis of ESCC. Updated guidelines from the National Comprehensive Cancer Network standardize the practice for the diagnosis and treatment of esophageal cancer. Patients with ESCC are treated endoscopically or with surgery, chemotherapy, or radiotherapy, based on tumor stage. Minimally invasive treatments help improve the quality of life of patients who undergo such treatments. We review recent developments in the diagnosis and treatment of ESCC and advances gained from basic and clinical research.

Keywords: Acetaldehyde; Aldehyde Dehydrogenase 2; Genetic Polymorphism; Field Cancerization; Squamous Differentiation.

Esophageal cancer is the 8th most common cancer and the 6th leading cause of cancer-related mortality in the world,[1–3] with an estimated 456,000 new cases per year worldwide.[3] Esophageal cancer comprises 2 main histological subtypes: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma.[4] ESCC is the major histological type and accounts for 80% of cases of esophageal cancer worldwide.[2] The incidence of ESCC is high in specific ethnic groups and certain locations[5,6] and is affected by environmental factors (alcohol consumption and tobacco use) and genetic factors (mutations in enzymes that metabolize alcohol).[1]

Only 15% to 25% of patients with ESCC survive for 5 years after diagnosis.[7,8] Recent advances in image-enhanced endoscopy allow detection of early esophageal neoplastic lesions.[9] Advances in therapeutics such as endoscopic resection (ER), surgery, radiotherapy, and chemotherapy have led to substantial improvements in clinical management and outcomes.[1,7] We review recent multidisciplinary advances in basic and clinical studies of ESCC.

Epidemiology

The incidence of esophageal cancer is 3-fold higher in men than women,[3] and approximately 80% of cases occur in developing countries.[3] The incidence of esophageal cancer varies greatly with location.[5] There is a high prevalence of ESCC in east Asia, eastern and southern Africa, and southern Europe.[5,10] In contrast, the incidence of ESCC is low in North America and other parts of Europe.[6] These variations indicate that ethnic and genetic factors and lifestyle all have roles in the development of ESCC.

Alcohol consumption and tobacco use are established risk factors for ESCC[7] and have synergistic effects on risk.[11] Acetaldehyde associated with alcohol intake was added as a definite carcinogen (a group 1 carcinogen) for the esophagus by the International Agency for Research on Cancer.[12] Purported risk factors for ESCC include low levels of consumption of fruits and vegetables; deficiency of selenium,

Abbreviations used in this paper: **ADH1B, alcohol dehydrogenase 1B; ALDH2, aldehyde dehydrogenase 2; CRT, chemoradiotherapy; CT, computed tomography; CYP, cytochrome P450; DCF, docetaxel and cisplatin plus 5-fluorouracil; dG, deoxyguanosine; EGFR, epidermal growth factor receptor; ER, endoscopic resection; ESCC, esophageal squamous cell carcinoma; EUS, endoscopic ultrasonography; FA, Fanconi anemia; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; 5-FU, 5-fluorouracil; GST, glutathione *S*-transferase; HGIN, high-grade intraepithelial neoplasia; HPV, human papillomavirus; IPCL, intrapapillary capillary loop; LGIN, low-grade intraepithelial neoplasia; LVL, Lugol-voiding lesion; NBI, narrow band imaging; SCC, squamous cell carcinoma; SEMS, self-expanding metal stent.**

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zinc, or vitamin E; high levels of exposure to areca nuts or polycystic aromatic hydrocarbons; and poor oral hygiene.[1,12] Meta-analyses have found evidence for the involvement of human papillomavirus (HPV) infection in ESCC.[13,14]

Alcohol, Acetaldehyde, and Carcinogenesis

Ingested alcohol is absorbed from the upper gastrointestinal tract and transported to the liver, where it is metabolized to acetaldehyde (intrinsic acetaldehyde) by alcohol dehydrogenase 1B (ADH1B). Acetaldehyde is subsequently detoxified to acetic acid by aldehyde dehydrogenase 2 (ALDH2) (Figure 1).[15] ALDH2 activity is reduced by the polymorphism Glu504Lys,[16] which is prevalent in Mongoloid but not in Caucasoid or Negroid populations[17]; it increases blood, salivary, and breath levels of acetaldehyde after alcohol intake.[18,19] Heavy ingestion of alcohol increases the risk of ESCC in people with the ALDH2 Glu504Lys polymorphism.[20] This finding could account for the higher incidence of ESCC in Asian versus Western countries.

Acetaldehyde is an organic compound found in ripe fruits, bread, coffee, cheese, and yogurt,[21] alcoholic beverages,[21] and tobacco smoke.[22] Alcoholic beverages such as Calvados and other spirits contain particularly high amounts of acetaldehyde, and frequent consumption of these beverages is associated with an increased risk of ESCC.[23] Acetaldehyde can also be generated in the human oral cavity by microorganisms such as yeasts and bacteria.[24–26] Acetaldehyde from alcoholic beverages, foods, and/or oral microflora could therefore provide a potential source of carcinogens that predispose people to ESCC (Figure 1).

Numerous in vitro and in vivo studies support the mutagenic and carcinogenic effects of acetaldehyde.[27] Acetaldehyde causes single- and double-strand DNA breaks,[28] point mutations,[29] sister chromatid exchanges, and gross chromosomal aberrations.[30,31] Acetaldehyde also binds to proteins to cause structural and functional alterations.[27] Many of the altered enzymes are involved in DNA repair, DNA methylation, and the antioxidative defense system.[32,33] Studies of inhalation in rats and hamsters show that acetaldehyde causes nasal carcinoma and respiratory squamous cell carcinoma (SCC).[34,35]

Acetaldehyde reacts with DNA to form DNA adducts.[36] A single molecule of acetaldehyde reacts with deoxyguanosine (dG) to generate N^2-ethylidene-2′-dG, which can be stabilized by reduction to the product N^2-ethyl-2′-dG (Figure 2).[36] Because N^2-ethylidene-2′-dG is the direct and most abundant DNA adduct derived from acetaldehyde, it is a specific biomarker for identifying acetaldehyde-derived DNA damage.[37] N^2-ethyl-2′-dG inhibits trans-lesion DNA synthesis, which leads to replication errors and/or frameshift deletion mutations.[38] Another class of DNA adducts, N^2-propano-2′-dG, which is derived from 2 molecules of acetaldehyde (Figure 2), has also been shown to be mutagenic.[39,40] However, the mechanistic role of DNA adducts in acetaldehyde-related ESCC carcinogenesis is unclear.[36]

Exposure of human normal fibroblasts to acetaldehyde induces mutations (most frequently G:C→A:T transitions) in the tumor suppressor gene *TP53*.[41] This transition pattern is consistent with that found in a study of the *HPRT* reporter gene.[29] Additionally, the G:C→T:A transition is the second most frequent acetaldehyde-mediated mutation in *TP53*, indicating that G:C base pairs are a specific target of acetaldehyde-induced damage.[41] Given that acetaldehyde reacts with dG to generate DNA adducts such as N^2-ethylidene-2′-dG and N^2-propano-2′-dG, guanine might be a specific target of acetaldehyde. These findings support the idea that exposure to acetaldehyde contributes to development of ESCC.

Tobacco and Carcinogenesis

A large-scale, population-based cohort study revealed that past smokers (adjusted hazard ratio, 3.27) as well as current smokers (adjusted hazard ratio, 3.69) have a higher risk of ESCC than never smokers.[42] Among current smokers, pack-years and cigarettes per day are also associated with the incidence of ESCC, with the risk increasing in a dose-dependent manner.[42]

Tobacco smoke contains carcinogenic substances such as nicotine-derived nitrosamine ketone and *N*′-nitrosonornicotine, which are called tobacco-specific nitrosamines[43]; direct contact between these carcinogens and the esophageal mucosa has been proposed to increase the risk of ESCC. Polycyclic aromatic hydrocarbons and aromatic amines are also major classes of carcinogens present in tobacco and tobacco smoke.[44] They are converted into DNA-reactive metabolites by cytochrome P450 (CYP)-related enzymes and then subjected to detoxification by glutathione *S*-transferases (GSTs).[44] Genetic polymorphisms of these enzymes (eg, *CYP1A1*,[45–47] *GSTM1*,[45] and *GSTP1*[48]) have been associated with the risk of esophageal cancer,[49] and a meta-analysis revealed that people with Ile to Val substitution encoded in the *CYP1A1* gene have an increased risk of esophageal cancer.[50] Tobacco smoke contains the carcinogen acetaldehyde,[51] so alcohol consumption and tobacco smoking are considered to increase the risk of ESCC synergistically in people with specific polymorphisms in *ADH1B* and *ALDH2*.[52]

Development of ESCC

ESCC develops via a multistep process that begins with a normal squamous epithelium and progresses to low-grade intraepithelial neoplasia (LGIN), high-grade intraepithelial neoplasia (HGIN), and ultimately to invasive carcinoma (Figure 3*A*).[53] LGIN, HGIN, and invasive ESCC can be visualized as Lugol-voiding lesions (LVLs) by Lugol chromoendoscopy.[54,55] The staining pattern of LVLs varies from an absence of LVLs to numerous irregularly shaped multiform LVLs (Figure 3*B*).

ESCC occurs synchronously and/or metachronously in conjunction with head and neck SCC. This association can be explained by the phenomenon of field cancerization.[56] A polyclonal mutation in *p53* is believed to be a mechanism

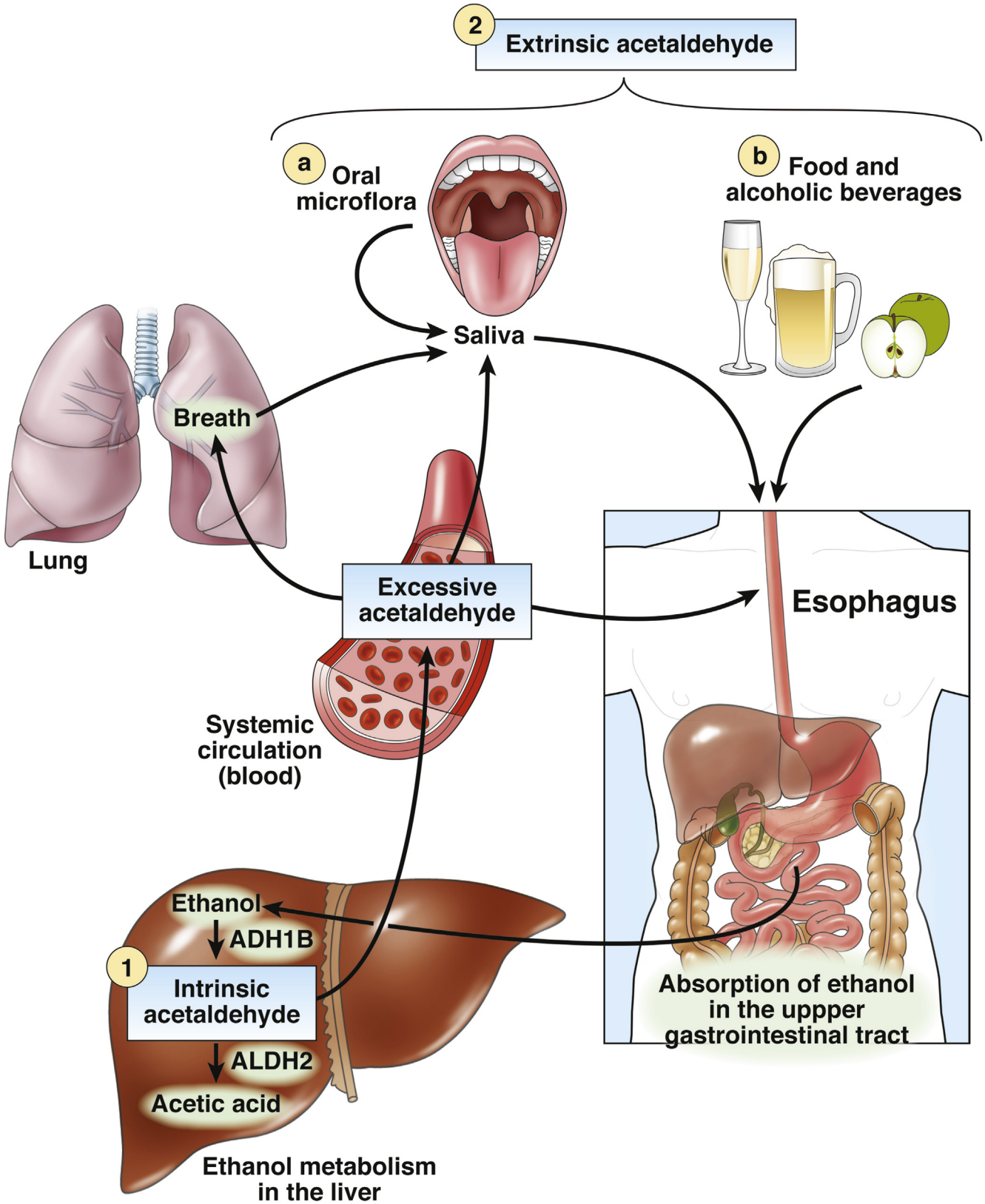

Figure 1. The source of acetaldehyde. The esophageal epithelium is exposed to carcinogenic acetaldehyde via (*1*) intrinsic and (*2*) extrinsic pathways. (*1*) Intrinsic acetaldehyde derived from ethanol metabolism in the liver. Ethanol is absorbed in the upper gastrointestinal tract and is metabolized to acetaldehyde by ADH1B in the liver. Subsequently, acetaldehyde is degraded to acetic acid by ALDH2. Acetaldehyde that exceeds its degrading activity in the liver circulates throughout the entire body, including the esophagus, lungs, and salivary glands. (*2*) Extrinsic acetaldehyde derived from alcoholic beverages and foods (*a*) and that produced by oral microflora (*b*). Extrinsic acetaldehyde is believed to be associated with direct exposure to the esophageal epithelium.

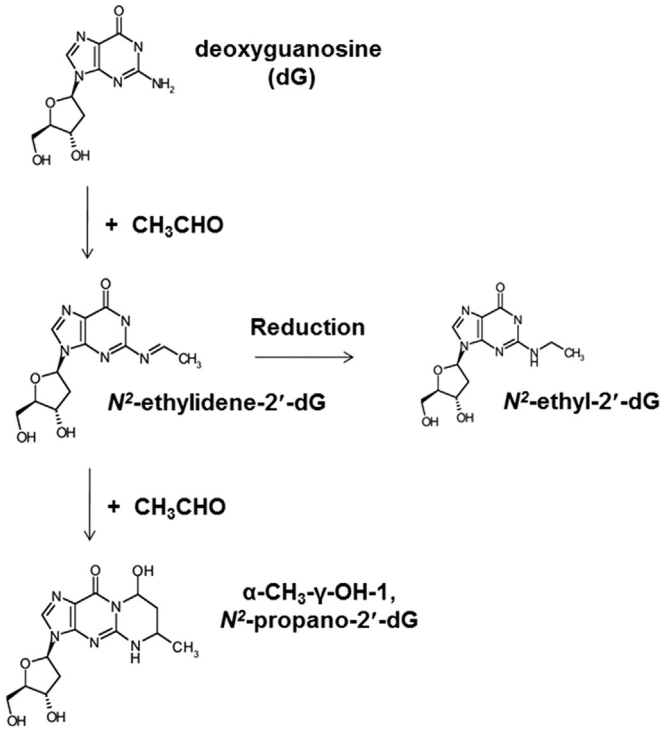

Figure 2. Formation of acetaldehyde-derived DNA adducts. A single molecule of acetaldehyde reacts with dG to form N^2-ethylidene-2′-dG, which is reduced to N^2-ethyl-2′-dG. The reaction of acetaldehyde with N^2-ethylidene-dG results in the formation of α-CH_3-γ-OH-1, N^2-propano-2′-dG.

involved in field cancerization.[57] A polymorphism in *ALDH2* has also been related to the occurrence of multiple LVLs and multiple SCCs in the esophagus and the head and neck.[58] Again, acetaldehyde is considered to have a key role in field cancerization of the squamous epithelium.

Pathology

In histopathologic analyses, ESCC is defined based on mitotic activity, nuclear atypia, and degree of squamous differentiation.[53] Consequently, ESCC is classified as well-differentiated SCC, moderately differentiated SCC, poorly differentiated SCC, and undifferentiated SCC (Figure 4) (World Health Organization classifications).[53] The histopathologic grade is incorporated into the TNM classification as a factor (G categories: G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; G4, undifferentiated) that is used to determine prognosis.[59] Involucrin is expressed in well-differentiated ESCC tumor nests but not in poorly differentiated ESCC, and it is considered to be a marker of the differentiation grade of ESCC tissues.[60,61] Because inhibition of squamous differentiation promotes tumor development in xenograft models,[60] squamous differentiation might affect the malignant potential of individual ESCC cells.

Genetics

Genes that Regulate the Cell Cycle or Differentiation

Analyses of comprehensive mutational catalogues using high-throughput sequencing technologies have revealed widespread genomic alterations in ESCC (Table 1).[62–65] The first large-scale comprehensive analysis, which was conducted using whole genome sequencing, whole exome sequencing, and array-based comparative genomic hybridization, showed that more than 83% of ESCCs contained a somatic mutation in *TP53*.[62] The highest frequency of mutation was in *TP53* (59%–93% of all patients), confirmed by other large-scale whole genome or whole exome sequencing analyses.[63–65] Mutation of *TP53* has therefore been proposed as a key factor in the development of ESCC.

Mutations in other cell genes that regulate the cell cycle (*CDKN2A* [encodes p16], *RB1*, *NFE2L2*, *CHEK1*, and *CHEK2*) or differentiation (*NOTCH1* and *NOTCH3*) have been detected in 2% to 10% of ESCCs.[62–64] Moreover, many genes that regulate the cell cycle are also amplified in ESCCs (*CCND1* in 46.4% of cases, *CDK4/CDK6* in 23.6% of cases, and *MDM2* in 5.7% of cases),[62] implicating them in the development of ESCC.

Epidermal Growth Factor Receptor Signaling Pathway

Epidermal growth factor receptor (EGFR) is overexpressed in 59.6% to 76% of ESCCs[66,67] and is associated with a poor prognosis.[66,67] Large-scale sequencing studies have shown *EGFR* to be overexpressed (in 68% of tumors) and/or amplified (in 11%–24%)[62] but not frequently mutated (in 0–1.8% of ESCCs).[62–64] Moreover, 78.6% of ESCCs have mutations and/or amplifications in factors downstream of EGFR, such as RAS and AKT pathways.[62] EGFR signaling pathways are considered to be involved in the development of ESCC.

Somatic Mutational Signature

G:C→A:T transitions and G:C→C:G transversions are frequently detected in ESCC cells.[63,65] Interestingly, the G:C→A:T transition is a typical mutation signature induced by acetaldehyde.[29,41] Another mutation frequently detected in ESCC is that of cytosine in TpCpX trinucleotides.[65] This pattern corresponds to the mutation signature that can be induced by members of the APOBEC family,[68,69] which might reflect the increased APOBEC activity observed in ESCC cells.

Epigenetic Factors

Epigenetic alterations such as DNA methylation, histone modification, and loss of genome imprinting are involved in the development of ESCC, as for other neoplasms.[70] For instance, hypermethylation of promoter regions of *APC*, *RB1*, and *CDKN2A* has been detected in ESCCs.[71–73] Methylation of *CDKN2A,* whose product p16 regulates *RB1*, is associated

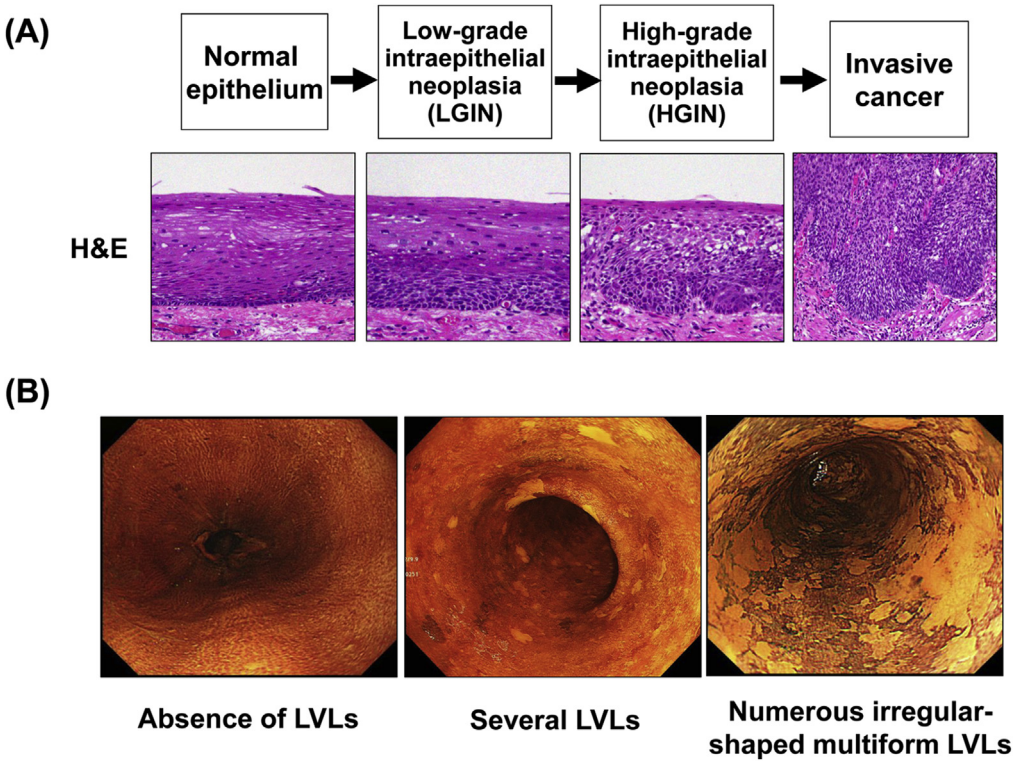

Figure 3. Scheme of the dysplasia-carcinoma sequence. (*A*) Images of H&E staining in tissues representing normal epithelium, LGIN, HGIN, and invasive cancer. An increased number of basal cells and mild cytological atypia are seen in LGIN, whereas architectural disarray, loss of polarity, and cellular atypia (greater than that seen in LGIN) are evident in HGIN. These stages are considered to develop progressively. (*B*) Representative endoscopic views of Lugol chromoendoscopy showing no LVLs, several LVLs, and many irregularly shaped multiform LVLs.

with p53 overexpression.[74] These cycle-regulatory pathways appear to interact to promote the development of ESCC.

Mutations in genes that regulate histone modification have been observed in approximately 63% of ESCCs (mutations in *MLL2* detected in 19%, in *EP300* in 10%, in *MLL3* in 6%, and in *CREBBP* in 6%).[64] In addition, members of the SWI/SNF complex, which is involved in epigenetic regulation, are mutated in ESCCs (mutations in *ARID* detected in 5%, in *PBRM1* detected in 5%, and in *ARID1A* detected in 1%).[63]

Hereditary ESCC

Tylosis esophageal cancer, also known as Howel–Evans syndrome, is a rare familial cancer syndrome inherited in an autosomal dominant manner and characterized by hyperkeratosis of the palms or soles. People with this syndrome have a high risk of esophageal cancer.[75] More than 90% of patients with this syndrome develop ESCC by the time they are 65 years old.[76] Missense mutation of rhomboid family member gene 2 (*RHBDF2*), which is involved in the activation of EGFR signaling, has been found to cause this syndrome.[75]

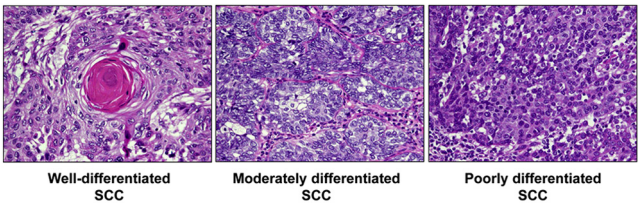

Figure 4. Representative histopathologic images of ESCC. ESCC is graded based on mitotic activity, nuclear atypia, and degree of squamous differentiation. (*Left panel*) Well-differentiated SCC. (*Middle panel*) Moderately differentiated SCC. (*Right panel*) Poorly differentiated SCC.

Polymorphisms

Polymorphisms in genes such as *TP53*,[77] *MDM21*,[77] *CASP8*,[78] and *COX2*[79] are associated with the risk of ESCC. Recent genome-wide association study–based analyses of patients with ESCC detected several single nucleotide polymorphisms that appear to be risk factors for ESCC. These include rs4135113, which regulates nonsynonymous coding in base excision repair; rs1800450, which regulates monosaccharide binding; and rs3769823, which regulates CASP8.[80] These single nucleotide polymorphisms are considered to be associated with susceptibility to ESCC.[80] Moreover, an integration analysis of 3 genome-wide association studies, comprising more than 9000 cases of ESCC, associated the single nucleotide polymorphisms rs7447927 (located at 5q31.2) and rs1642764 (located at 17p13.1) with ESCC.[81]

Fanconi Anemia Pathway

Fanconi anemia (FA) is an autosomal recessive disorder characterized by genomic instability, bone marrow failure, developmental defects, and early development of cancers such as hematologic malignancies and SCCs of the uterine cervix, head and neck, and esophagus.[82] FA is caused by mutations in genes that regulate the FA pathway, which

Table 1. Recent Results of Comprehensive Analyses of Genetic Alterations Using High-Throughput Sequencing

No. of patients (method)	Ethnic group	Genomic alterations	Authors
17 (WGS), 71 (WES), 123 (CGH)	Chinese	*TP53, RB1, CDKN2A (p16), NFE2L2, CHEK1, CHEK2, PIK3CA, NOTCH1, NOTCH3, CCND1, CDK4/CDK6, MDM2, EGFR*	Song et al[62]
20 (WES), 119 (targeted seq), 4 (RNA seq)	Chinese	*TP53, RB1,CDKN2A (p16), NFE2L2, PIK3CA, NOTCH1, NOTCH3, ARID2, EGFR, RTK/RAS* signaling pathways	Lin et al[63]
118 (WES)	Chinese	*TP53, RB1, CDKN2A (p16), NFE2L2, CCND1, EGFR, histone-modifying genes (MLL2, MLL3, CREBBP)*	Gao et al[64]
14 (WGS), 90 (WES)	Chinese	*TP53, CDKN2A (p16), PIK3CA, and mutational signature*	Zhang et al[65]

WGS, whole-genome sequencing; WES, whole-exome sequencing; CGH, comparative genomic hybridization; seq, sequencing.

controls replicon-dependent removal of interstrand DNA cross-links. The FA pathway is studied during research on DNA repair, cancer progression, and protein ubiquitination in response to genotoxic insults.[83] FANCD2, a factor in the FA pathway, counteracts acetaldehyde-induced genotoxicity in mice.[84] Moreover, germline mutations in *FANCD1* (*BRCA2*) are also found in patients with a familial history of ESCC.[85] These results indicate that the role of the FA pathway in ESCC caused by acetaldehyde-mediated DNA damage.

HPV

HPV promotes carcinogenesis through the action of oncoproteins E6 and E7, which target numerous cellular pathways, including the inactivation of p53 and retinoblastoma protein.[86] HPV infection is associated with tumorigenesis in cervical cancer as well as in head and neck SCC.[87] However, a relationship between HPV infection and development of ESCC has not been observed consistently.[53] A comprehensive genetic analysis found no correlation between HPV infection and ESCC.[62] In contrast, a meta-analysis reported the prevalence of HPV in patients with ESCC to be as high as 32.2%.[13] Africa and Asia have the highest prevalence of HPV; specific Chinese provinces with a high prevalence of HPV have a particularly high incidence of ESCC.[13] There is controversy over whether HPV infection is associated with the development of ESCC.

Mechanisms of Invasion and Metastasis

A recent study associated amplification of the eukaryotic initiation factor 5A2 gene (*eIF5A2*) with ESCC invasiveness and metastasis of ESCC via hypoxia.[88] *eIF5A2* could promote the epithelial-to-mesenchymal transition and increase the migratory and invasive capacities of esophageal cells.[88]

A 3-dimensional organotypic culture system can be used to investigate the mechanisms of invasion based on interactions between the epithelium and stroma.[89] Researchers have used this model to identify several genes and signaling pathways that regulate esophageal cell invasion. Overexpression of EGFR and inactivation of p53 in esophageal epithelial cells expand a cell subpopulation via upregulation of zinc finger E-box binding transcription factors that can undergo the epithelial-to-mesenchymal transition.[90] These cells have an invasive phenotype in the stromal matrix, accompanied by increases in activation of the RTK cMET.[91,92] Moreover, microarray analysis of RNA extracted by laser capture microdissection from invading cells grown in 3-dimensional organotypic culture, compared with non-invading cells, identified several genes that might facilitate tumor invasion. These genes include insulin-like growth factor–binding protein 3,[93] periostin,[94] and *WNT10A*.[95] Furthermore, stromal fibroblasts regulate the invasive activities of ESCC cells; fibroblast-secreted hepatocyte growth factor, the ligand of c-MET, helps create an environment conducive to tumor invasion.[92]

Diagnosis and Staging

Imaging modalities such as endoscopy, endoscopic ultrasonography (EUS), esophagography, computed tomography (CT), and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) are used in the diagnosis and staging of ESCC. Endoscopy is the most sensitive modality for the detection and diagnosis of esophageal neoplasia. The use of endoscopic screening and treatment has contributed to reductions in ESCC-associated mortality.[96] EUS, esophagography, CT, and FDG-PET are used to assess the depth of invasion in the esophageal wall, length of tumors, direct invasion to adjacent organs, and lymph node and distant metastasis.[97]

Endoscopy

Advanced ESCC is found as a protruding mass or a depressed ulcer. Superficial ESCC is often difficult to identify because of minimal macroscopic and color changes, but it is usually observed as an uneven surface with a thin white coating or a reddish color change on the mucosal surface.[98]

Iodine has an affinity for glycogen in the nonkeratinized squamous epithelium and stains the normal epithelium a mahogany brown color; the cancerous epithelium is devoid of staining because it lacks glycogen.[99] Lugol solution, which contains iodine, was first introduced as Schiller test for the detection of SCC in the uterine cervix[99] and is now used in

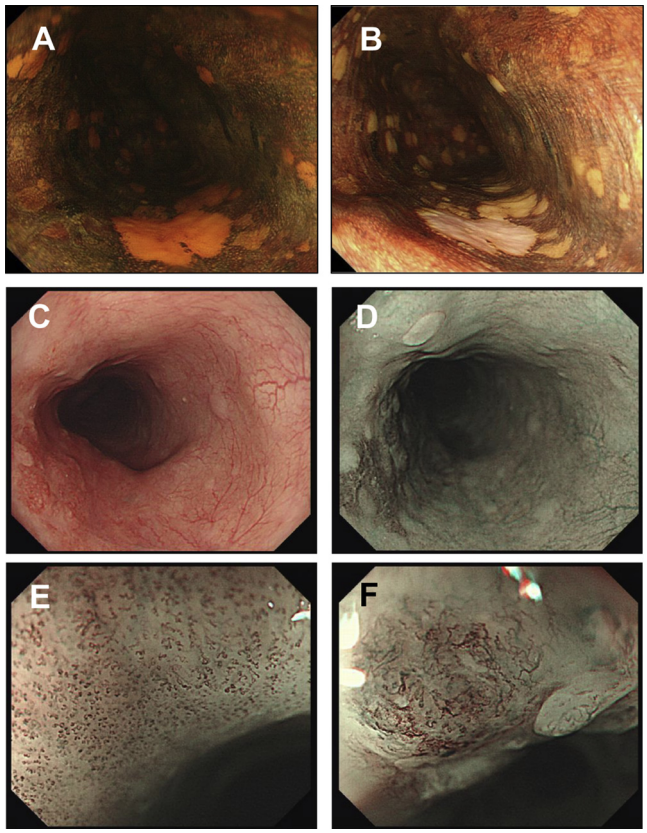

Figure 5. Diagnosis of superficial ESCC using endoscopy. (*A*) Lugol chromoendoscopy. Immediately after Lugol staining, cancerous lesions are seen as LVLs. (*B*) Pink color sign. Definite cancerous lesions show the pink color sign a few minutes after Lugol staining. (*C*) White light imaging of superficial ESCC. A reddish flat lesion is seen in the posterior wall of the esophagus. (*D*) NBI identifies the same lesion clearly as a well-demarcated brownish area. (*E*) Representative images of IPCLs. Magnifying NBI showed looped IPCL with morphological changes of dilation, meandering, irregular caliber, and nonuniformity. These findings indicate that the depth of the tumor is Tis or T1a lamina propria mucosa. (*F*) Nonlooped IPCLs. Magnifying NBI showed nonlooped IPCL characterized by extension and advanced destruction of looped IPCLs and/or generation of new tumor vessel. These findings indicate that the depth of the tumor is deeper than T1a muscularis mucosa.

Lugol chromoendoscopy to detect ESCC.[100] The pink color sign, a light-pink appearance of the iodine-unstained area a few minutes after iodine staining in Lugol chromoendoscopy (Figure 5*A* and *B*), is also useful for distinguishing SCC or HGIN from LGIN.[101] This appearance is based on the complete loss of the normal keratinous layers in the mucosal layers of HGIN.[101] The sensitivity and specificity of the pink color sign for the discrimination of HGIN from LGIN are 92% and 94%, respectively.[101]

A narrow band imaging (NBI) system, which uses narrow band illumination of 415-nm and 540-nm wavelengths corresponding to the peaks of the absorption wavelengths of hemoglobin,[102] can detect superficial ESCC as a well-demarcated brownish area (Figure 5*C* and *D*).[103] Magnifying NBI clearly visualizes microvascular structures (intrapapillary capillary loops [IPCLs]) of the squamous epithelium and cancerous lesions (Figure 5*E* and *F*)[104] and is useful for identifying cancerous lesions by the changes in IPCLs.[104] A prospective, randomized, controlled study reported a higher detection rate of superficial SCC in the head and neck and the esophagus for NBI compared with conventional white light imaging (97% vs 55%).[103] NBI detects superficial cancer in the head and neck with 100% sensitivity, 78.6% specificity, 83.3% positive predictive value, 100% negative predictive value, and 86.7% accuracy. NBI detects cancer of the esophagus with 97.2% sensitivity, 42.1% specificity, 90.4% positive predictive value, 72.8% negative predictive value, and 88.9% accuracy.[103]

Staging

Staging of the tumor is important to determine the therapeutic strategy. The Union for International Cancer Control TNM classification (7th edition, 2009) is used widely to assess the anatomic extent of ESCC.[59]

The T stage is defined by the extent of the primary tumor and is classified as one of 5 categories: Tis (carcinoma in situ or high-grade dysplasia; eg, intraepithelial tumor), T1 (T1a, tumor invading the lamina propria or muscularis mucosae; T1b, tumor invading the submucosa), T2 (tumor invading the muscularis propria), T3 (tumor invading the adventitia), and T4 (tumor invading the adjacent structures: T4a, tumor invading the pleura, pericardium, or diaphragm; T4b, tumor invading other adjacent structures such as the aorta, vertebral body, or trachea).[59] Endoscopy, EUS, esophagography, and CT are used for T staging of tumors.

Macroscopic findings on endoscopy are useful for the assessment of tumor depth of superficial ESCC. According to the Japanese Classification of Esophageal Cancer,[98] superficial (type 0) cancers are classified into types 0-I (superficial and protruding type), 0-II (superficial and flat type: a lesion without definite protrusion or depression), and 0-III (superficial and excavated type). 0-I lesions and 0-III lesions are believed to have high probabilities (94.7% and 100%, respectively) of invading up to the submucosal layers (T1b stage). Most 0-IIa (slightly elevated type) and 0-IIb (flat type) tumors are Tis or T1a cancers, whereas 0-IIc (slightly depressed type) tumors are widely distributed from Tis to T1b cancers.[105]

The depth of cancer invasion is described according to the IPCL classification pattern by NBI with magnification.[104] Magnifying NBI can differentiate intramucosal cancers (Tis or T1a) from submucosal (T1b) cancers with high levels of sensitivity (78%) and specificity (95%).[106] Visualization of the microvascular structure of the tumors by magnifying NBI is therefore a useful tool for the differential diagnosis of T1a from T1b cancers.

Esophagography is used for evaluating the shape, length, and location of tumor.[107] EUS and CT are also used for evaluating the T stage of ESCC. EUS can identify the distinct tissue layers of the esophageal wall, and a tumor can be detected as a low echoic mass. EUS using a 20- to 30-MHz mini-probe is useful for diagnosing the tumor depth in superficial ESCC.[108]

As a limitation, EUS is unreliable for the staging of tumors with stenotic lesions or after neoadjuvant chemotherapy.[109,110] CT also has limitations for determining the exact depth of a tumor within the esophageal wall and thus cannot differentiate between T1, T2, and T3, although CT is useful for discriminating T3 and T4 regions.[111] The accuracy of CT for T4b staging in terms of aortic and tracheobronchial invasion is approximately 80%.[112,113] When tracheobronchial invasion is suspected, bronchoscopy and biopsy should be considered to confirm the diagnosis.

N-stage tumors (spread to regional lymph nodes) are defined by the number of involved regional nodes, including celiac axis nodes and cervical paraesophageal nodes but not supraclavicular nodes. The categories are N0 (no regional lymph node metastasis), N1 (metastasis in 1–2 regional lymph nodes), N2 (metastasis in 3–6 regional lymph nodes), and N3 (metastasis in $\geq$7 regional lymph nodes).[59] EUS and CT are used to determine the presence of involved regional lymph nodes in patients with ESCC. In a meta-analysis to compare the diagnostic performance of EUS and CT in N staging, the sensitivity and specificity values for EUS were 80% and 70%, respectively; those of CT were 50% and 83%, respectively.[114]

M-stage tumors are classified as M0 (no distant metastasis) and M1 (distant metastasis).[59] Contrast-enhanced CT is the most commonly used imaging modality to detect distant metastasis, and masses in the liver larger than 1 cm are likely to be hepatic metastatic lesions. The sensitivity of contrast-enhanced CT for detecting metastasis is as high as 90%.[115]

FDG-PET is of value in the detection of distant metastasis at the initial staging of esophageal cancer as well as in the assessment of the response to induction chemotherapy.[116,117] However, FDG-PET has a low sensitivity for initial nodal staging,[116] and it is unclear whether FDG-PET is useful in the assessment of recurrence after surgery.[118] Recently, coregistration of FDG-PET and CT using a combined system has been shown to be of additional value for image interpretation using both modalities.[118] This dual-imaging modality allows clinicians to evaluate tumors functionally and structurally,[119] improves the accuracy of FDG-PET imaging in esophageal cancer, and provides useful data of diagnostic and therapeutic significance for clinical management.[118]

Treatment

There are many different approaches to the treatment of patients with ESCC, including endoscopic therapy, surgery, chemotherapy, and radiotherapy. To facilitate the standard practice of therapeutics based on the principle of evidence-based medicine, updated guidelines for esophageal cancers are published by the National Comprehensive Cancer Network.[97] The Japan Esophageal Society has also edited guidelines for the diagnosis and treatment of esophageal carcinoma.[120]

Endoscopic Resection and Ablation

Early-stage ESCC (Tis and T1a), with negligible risk of metastasis to the lymph node, can be cured by endoscopic local treatment, such as ER and/or an ablative method (eg, radiofrequency ablation or photodynamic therapy).[97] Before endoscopic treatment, the depth of invasion, horizontal spread, and presence or absence of multifocal lesions should be characterized fully. The depth of invasion is closely associated with lymph node metastasis, and the frequency of lymph node metastasis in mucosal ESCC is reported to be 3%.[121] However, the accuracy of pretreatment diagnosis regarding the depth of invasion using EUS and/or magnifying NBI is limited. To accurately determine the depth of invasion, diagnostic ER can be used. Endoscopic submucosal dissection gives an accurate pathological diagnosis because of the high rate of en bloc resection, irrespective of the tumor size, despite the high incidence of bleeding or perforation.[122] ER is a standard, minimally invasive treatment for Tis and T1a ESCC.[97] The indication of ER for T1b ESCC is controversial; a study is under way to provide the rationale to address this issue.[123] This study concept is as follows: ER therapy alone can be effective for patients with a Tis or T1a tumor with a negative surgical margin and without lymphatic or venous invasion, but additional treatment, including surgical resection or chemoradiotherapy (CRT), should be considered for patients with a T1b tumor and/or positive surgical margin and/or positive lymphatic/venous invasion.

Endoscopic surveillance after endoscopic local therapy for early-stage ESCC should be continued because metachronous ESCC and head and neck SCC can develop, especially in patients with multiple LVLs.[58] Additional ER and/or ablation may be needed if metachronous early-stage ESCC is detected. Patients should be evaluated every 3 months in the first year after treatment and every 3 to 6 months in the second year.[97]

Surgery

Surgery is used widely to obtain locoregional control and has an important role in the treatment of esophageal cancer. Transthoracic esophagectomy is one of the most invasive surgeries. Outcomes appear to be related to the incidence and management of perioperative complications and seem to be good in high-volume centers with experienced surgeons.[124] ESCC is often accompanied by extensive metastasis to lymph nodes in the cervical, thoracic, and abdominal regions. There is controversy regarding the extent of lymph node dissection required. In particular, the advantage of a 3-field lymphadenectomy over a 2-field lymphadenectomy for ESCC is unclear. A recent meta-analysis of 13 studies revealed a marked improvement in surgical outcomes after 3-field lymphadenectomy compared with 2-field lymphadenectomy, including a higher 5-year rate of survival (hazard ratio, 0.64).[125] On the other hand, perioperative morbidities have been noted, such as a higher prevalence of anastomotic leakage and a similar prevalence of pulmonary complications and postoperative vocal cord palsy.[125] The addition of cervical lymph node dissection therefore improves the long-term outcomes of patients compared with only 2-field lymphadenectomy, especially for patients with thoracic esophageal cancer with positive lymph nodes.

However, 3-field lymphadenectomy is regarded to be the more invasive procedure.[125]

To overcome this issue, minimally invasive surgery has been developed. Magnifying the view from the thoracoscope makes it possible to perform accurate lymph node dissection; this technique has been applied to patients with stage I, II, and III (excluding T4) esophageal cancers. Some evidence is available on the short-term benefits (shorter hospital stays as well as lower rates of respiratory complications and total morbidity) of minimally invasive surgery compared with open esophagectomy.[126,127] Moreover, the rate of 5-year survival after minimally invasive esophagectomy is similar to that for open esophagectomy.[128] A prospective randomized trial is under way in Japan to prove the noninferiority of minimally invasive thoracoscopic esophagectomy to open esophagectomy for thoracic esophageal cancers.

Neoadjuvant and Adjuvant Therapy

Neoadjuvant chemotherapy (in the United Kingdom) or neoadjuvant CRT (in the United States and France) is performed as standard treatment for locally advanced ESCC.[129,130] However, clinical trials conducted in Europe and the United States have included a low percentage of patients with SCC (<50%). Randomized multicenter trials of patients with stage I/II ESCC that compared neoadjuvant CRT (cisplatin + 37-Gy radiation) followed by surgery with surgery alone showed that neoadjuvant CRT did not increase overall survival.[131] However, a recently updated meta-analysis (24 trials, 4188 patients, 3500 events, 65% of patients with SCC) provided strong evidence that neoadjuvant CRT and chemotherapy increase survival versus surgery alone (hazard ratios of 0.78 and 0.87, respectively) in patients with esophageal cancer, although a clear advantage of neoadjuvant CRT over neoadjuvant chemotherapy has not been shown.[132] Of note, when limited to the patients with ESCC included in this meta-analysis, neoadjuvant CRT significantly increased the chances of survival versus surgery alone (hazard ratio, 0.80) but not versus neoadjuvant chemotherapy (hazard ratio, 0.92).[132]

In Japan, neoadjuvant chemotherapy with cisplatin plus 5-fluorouracil (5-FU) is the standard treatment regimen for locally advanced (stage II or III, except T4) ESCC.[133] This neoadjuvant chemotherapy increases overall survival and is regarded as the standard treatment for patients with stage II or III ESCC (55% survive for 5 years).[134] Based on this background, another intensive neoadjuvant chemotherapeutic regimen with docetaxel and cisplatin plus 5-FU (DCF) has been proposed.[135] A phase 3 trial is under way to investigate whether DCF is superior to cisplatin plus 5-FU and whether cisplatin plus 5-FU with CRT is superior to cisplatin plus 5-FU alone.[136]

Interestingly, a German trial reported that the addition of surgery did not prolong survival of patients with locally advanced thoracic ESCC (T3-4N0-1M0) who responded to neoadjuvant chemotherapy followed by CRT.[137] In this trial, a tumor response to neoadjuvant chemotherapy was the single prognostic factor for overall survival.[137] A trial in France also reported that the addition of surgery did not prolong survival of patients with locally advanced thoracic esophageal cancer (T3-N0-1M0; 89% of patients with SCC) who responded to induction CRT.[138] These results indicate that good responses to neoadjuvant chemotherapy or CRT may not require additional surgery.

Definitive CRT

Because CRT has been reported to be superior to radiotherapy alone for the treatment of patients with locally advanced esophageal cancer,[139] the concept of definitive CRT has emerged. At first, definitive CRT was applied to inoperable locally advanced (T4) ESCC. Even for T4 ESCC, definitive CRT can produce complete remission in 15% to 33% of patients (median survival time of approximately 10 months).[140,141]

A clinical trial of definitive CRT, which included patients with stage II or III ESCC, reported a complete response in 68% of patients and that 37% survived for 5 years.[142] This result was inferior to that of neoadjuvant chemotherapy followed by surgery (5-year rate of survival, 55%).[134] Definitive CRT for stage II or III ESCC is therefore a nonsurgical treatment option.

CRT has some problems. First, CRT fails in more than 40% of patients[143]; the prognosis is poor for these patients, with more than 50% mortality within 6 months.[144] In such cases, salvage treatment is needed. Second, approximately 10% of patients with complete responses after treatment with 60-Gy CRT experience late-stage, high-grade toxicity, including pericarditis, pleural effusion, and radiation pneumonitis.[145] A dose-escalation study of radiation was conducted to improve local control.[146] However, no significant difference was observed in local/regional control of patients (85% of patients with SCC) treated with cisplatin plus 5-FU in the 50.4-Gy group versus the 64.8-Gy group.[146] Based on this evidence, the standard radiation dose of definitive CRT for ESCC is currently 50 to 50.4 Gy at 1.8 to 2 Gy per fraction. In addition, the use of the multiple-field technique to reduce the volume of the heart within the radiation field is recommended to prevent late-stage cardiac toxicity.

Salvage Therapy

The diagnosis of local recurrence after CRT should be conducted promptly and precisely. The median time to local recurrence after CRT is 9 months.[147] Early recurrent tumors that have achieved complete remission after CRT typically show a submucosal tumor–like appearance (Figure 6).[148]

Salvage therapies, including ER and surgery, are considered for residual or recurrent tumors after definitive CRT.[149] Salvage ER has been tested on residual and recurrent tumors at primary sites after definitive CRT and produced positive long-term results without severe complications in patients with superficial failed lesions.[150] Recently, photodynamic therapy has been shown to be a curative option for patients with local failure limited to the submucosal layer.[151] Salvage surgery is aimed at curative resection for those tumors. However, only patients with T1N0 or T2N0 ESCC survive for long periods.[144] Salvage

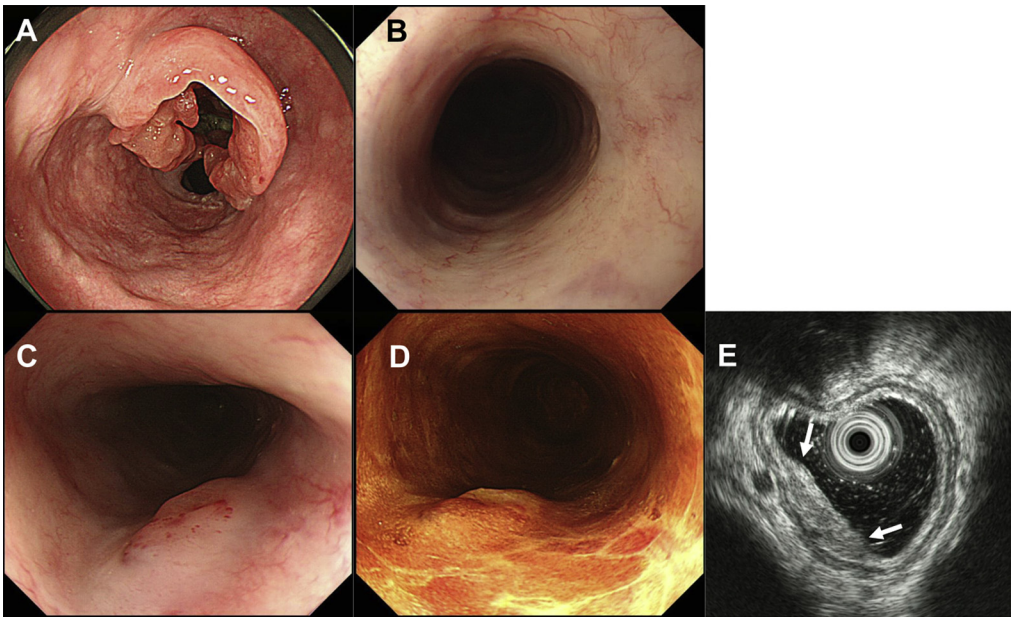

Figure 6. Submucosal tumor–like appearance of recurrent ESCC after chemoradiotherapy. (*A*) Endoscopic image at the initial diagnosis of ESCC. A large type 2 tumor is seen in the middle thoracic esophagus. (*B*) Endoscopic image after CRT. Complete response was achieved by definitive CRT. (*C*) Endoscopic image of a submucosal tumor–like recurrent tumor after complete response of the primary tumor. A submucosal tumor–like lesion was detected on a scar after CRT. (*D*) Lugol chromoendoscopic image of the tumor shown in *C*. The main part of the lesion was stained by Lugol staining, which indicates that the surface is covered in normal epithelium. (*E*) EUS image of the tumor shown in *C*. A low-echoic mass was found in the submucosa and in parts of the shallow layer of the muscularis propria.

surgery has a greater risk of respiratory complications and anastomotic leakage than planned surgery.[144,152] This risk is associated with fibrous changes in the mediastinum after radiation and difficulties in the anastomosis as a result of the irradiated gastric tubes.[144]

Chemotherapy for Unresectable Locally Advanced or Metastatic ESCC

Combinations of cisplatin and 5-FU are commonly used in chemotherapy for patients with unresectable locally advanced or metastatic ESCC; this treatment is believed to be better than the best supportive care.[153] Taxanes (docetaxel and paclitaxel) have been reported to be effective as single-agent chemotherapeutics, with response rates of 20% to 34%.[154,155] Recently, the 3-drug regimen with DCF was reported to have a 62% response rate.[156] Based on this result, a randomized controlled phase 3 study is under way to compare DCF with cisplatin plus 5-FU in patients with metastatic or recurrent ESCC.[157]

Targeted Therapy

EGFR is one of the most investigated molecular targets in the field of SCC. Cetuximab, a mouse-human monoclonal immunoglobulin G1 against EGFR, is effective against head and neck SCC in combination with radiotherapy.[158] However, addition of cetuximab to CRT did not yield a significant survival benefit for esophageal cancer, including ESCC, in a phase 3 study.[159] A phase 3 study of gefitinib, a tyrosine kinase EGFR inhibitor, in patients with ESCC did not show an increase in overall survival.[160] There is therefore little evidence to support EGFR-targeting therapies for ESCC.

Recently, strategies have been developed to target the programmed cell death protein 1 signaling pathway (PD1-PDL1).[161] Patients whose ESCC was positive for PD1 signaling (43.9%) had significantly poorer outcomes than patients whose ESCC did not have activation of this signaling pathway.[162] On the basis of these data, a clinical trial is under way to target the PD1-PDL1 pathway in patients with ESCC who have not responded to standard chemotherapy.

Palliative Care

Some patients with advanced ESCC experience dysphagia and malnutrition because of esophageal stenosis and aspiration caused by a fistula.[120] To improve these conditions, palliative care is strongly recommended.

Dysphagia and malnutrition decrease quality of life in patients with advanced ESCC.[163] Radiation therapy palliates dysphagia for several months, but it takes 4 to 6 weeks after treatment for symptoms to improve.[164] Instead, a self-expanding metal stent (SEMS) is a safe and effective treatment for palliation of dysphagia in patients with ESCC.[165] Compared with uncovered SEMSs, covered SEMSs prevent tumor growth (53% vs 100%) and reduce restenosis (8% vs 37%)[166] Biodegradable stents have been developed, although their application is limited because of unknown long-term efficacy.[167] In patients with prior CRT, SEMSs can cause life-threatening complications.[168]

Placement of a SEMS is also effective for closing malignant esophagorespiratory fistulas. SEMS were shown to sealed the esophagorespiratory fistula successfully in 80% (49/61) of patients.[169] Patients with successful closure with SEMSs survived longer than those with unsuccessful closure (15.1 vs 6.2 weeks).[169]

Future Directions

Alcohol, acetaldehyde associated with alcoholic beverages, and tobacco are esophageal carcinogens that contribute to the development of ESCC. Polymorphisms in ALDH2 also contribute to the development of ESCC, particularly in Asian people. In addition, external and internal risk factors together contribute to the development of ESCC. An effort is needed to develop preventive strategies as the next step. Advances in early detection should encourage the development of effective screening systems for high-risk people. Effective detection of early ESCC allows for the use of minimally invasive treatments such as ER. Field cancerization should be considered for intensive surveillance in successfully treated patients. However, for advanced ESCC, the treatment outcomes leave room for improvement. Further research is needed to establish techniques for less invasive surgery; more effective chemotherapy and radiotherapy are required to increase patient survival. Precision medicine based on genomic data could lead to new methods for prevention, diagnosis, and treatment of ESCC.

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