It is also mandatory to check for the development of either asynchronous remnant esophageal cancer or asynchronous multiple cancers of other organs such as of the stomach (gastric tube used for reconstruction) or head and neck region. Sato et al. reported that a second malignancy was the major cause of death among the patients without any lymph node metastasis who underwent an esophagectomy for thoracic esophageal cancer [18]. Therefore, endoscopic examinations are conducted for the head and neck region, remnant esophagus, stomach, and colorectum (see Fig. 1).

Conclusions

No standard follow-up method after a curative esophagectomy for esophageal cancer has yet been established. Furthermore, so far few studies have investigated the effectiveness of any follow-up schedules including the frequency and modalities used. The efficacy and suitability of the schedule shown in this article for the cure of patients with recurrence of esophageal cancer are not known. A nationwide accumulation of larger-scale clinical data based on a fixed schedule with a consensus is necessary to obtain evidence for the diagnosis and treatment of recurrent esophageal cancer. In the future, the performance of meta-analyses using the findings of many reports on postoperative follow-up are absolutely required.

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REVIEW ARTICLE

Alcohol drinking, cigarette smoking, and the development of squamous cell carcinoma of the esophagus: molecular mechanisms of carcinogenesis

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Abstract Esophageal cancer is the eighth most common incident cancer in the world and ranks sixth among all cancers in mortality. Esophageal cancers are classified into two histological types; esophageal squamous cell carcinoma (ESCC), and adenocarcinoma, and the incidences of these types show a striking variety of geographic distribution, possibly reflecting differences in exposure to specific environmental factors. Both alcohol consumption and cigarette smoking are major risk factors for the development of ESCC. Acetaldehyde is the most toxic ethanol metabolite in alcohol-associated carcinogenesis, while ethanol itself stimulates carcinogenesis by inhibiting DNA methylation and by interacting with retinoid metabolism. Cigarette smoke contains more than 60 carcinogens and there are strong links between some of these carcinogens and various smoking-induced cancers; these mechanisms are well established. Synergistic effects of cigarette smoking and alcohol consumption are also observed in carcinogenesis of the upper aerodigestive tract. Of note, intensive molecular biological studies have revealed the molecular mechanisms involved in the development of ESCC, including genetic and epigenetic alterations. However, a wide range of molecular changes is associated with ESCC, possibly because the esophagus is exposed to many kinds of carcinogens including alcohol and cigarette smoke, and it remains unclear which alterations are the most critical for esophageal carcinogenesis. This brief review summarizes the general mechanisms of alcohol- and smoking-induced carcinogenesis and then discusses the mechanisms of the development of ESCC, with special attention to alcohol consumption and cigarette smoking.

Keywords Esophageal squamous cell carcinoma · Carcinogenesis · Alcohol · Acetaldehyde · Smoking · Carcinogen · Molecular alterations

Introduction

The International Agency for Research on Cancer (IARC) has concluded from epidemiological data that the occurrence of malignant tumors of various organs, including the head and neck region, esophagus, liver, colorectum, and breast, is causally related to chronic alcohol consumption [1–3]. Cigarette smoking also causes more than one million cancer deaths per year in the world. About 90% of lung cancer is attributed to smoking [4–6]. The molecular mechanisms involved in alcohol- and smoking-related carcinogenesis have been clarified, although they are not fully understood [3, 5].

Although the precise etiology of cancers in the upper aerodigestive tract (UADT) (i.e., oral cavity, pharynx, larynx, and esophagus) still remains unclear, dietary and environmental factors are strongly implicated. Cigarette smoking and alcohol consumption are considered to be significant risk factors for esophageal squamous cell carcinoma (ESCC) [7–9]. Various kinds of genetic abnormalities have been investigated in ESCC, including the

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activation of oncogenes and inactivation of tumor-suppressor genes, and a large body of knowledge has been obtained concerning esophageal carcinogenesis [10, 11]. However, direct evidence showing a causal relationship of alcohol consumption or cigarette smoking with the genetic abnormalities observed in ESCC is insufficient. This brief review discusses the general molecular mechanisms of alcohol- and smoking-related carcinogenesis and then addresses the genetic alterations in ESCC, with attention to alcohol and cigarette smoke.

Molecular mechanism of alcohol-related carcinogenesis (Fig. 1)

Well-established carcinogens in alcohol and its metabolites

The mechanisms of ethanol-induced carcinogenesis are closely related to the metabolism of ethanol [3]. Ethanol is oxidized by alcohol dehydrogenase (ADH) in the liver, which results in the generation of acetaldehyde (AD). AD is then metabolized to acetate by aldehyde dehydrogenase-2 (ALDH2). AD is a carcinogen in various animals, because AD may induce gene mutations [3, 12]. Epidemiological studies clearly demonstrate that the inactive ALDH2 encoded by the *ALDH2*1/2*2* genotype, which causes an increased accumulation of AD following alcohol consumption, is a strong risk factor for the development of UADT cancers, in particular esophageal cancer [13, 14]. This fact indicates the carcinogenicity of AD.

There are unique mechanisms of topical AD production from local ethanol in the UADT [14]. Increasing alcohol consumption results in increasing AD concentration in the saliva which is higher than that in blood. The normal oral microflora can oxidize ethanol to AD, and this contributes to the AD level in the saliva. Moreover, because further metabolism of AD to acetate by oral bacteria is limited, the AD concentration in the saliva can be 10–100 times higher than that in the blood [15]. It is possible that AD is involved in UADT carcinogenesis, including carcinogenesis in the esophagus, because AD in saliva comes into direct contact with the mucosa of the UADT [3, 14].

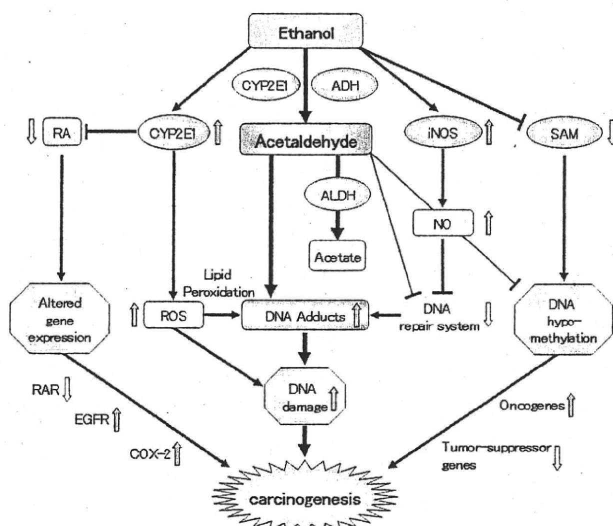

Fig. 1 Schematic presentation of ethanol metabolism and its role in carcinogenesis. *ADH* alcohol dehydrogenase, *CYP2E1* cytochrome P450 2E1, *ALDH* aldehyde dehydrogenase, *RA* retinoic acid, *RAR* RA receptor, *EGFR* epidermal growth factor receptor, *COX-2* cyclooxygenase-2, *ROS* reactive oxygen species, *iNOS* inducible nitric oxide synthase, *NO* nitric oxide, *SAM* *S*-adenosyl-L-methionine

General mechanisms of alcohol-induced carcinogenesis

AD interacts with DNA to form stable DNA adducts [3]. If AD-induced DNA adducts escape cellular repair mechanisms and persist, they may lead to miscoding, resulting in permanent gene mutations [16]. For example, AD causes point mutations in the hypoxanthine phosphoribosyltransferase (HPRT) 1 gene locus in human lymphocytes and induces sister chromatic exchanges and gross chromosomal aberrations [17, 18]. In fact, a high level of AD-DNA adducts has been found in lymphocyte DNA from alcoholic patients [19].

One of the important AD-induced DNA adducts is α-methyl-γ-OH-propano-deoxyguanosine (Cr-PdG). Cr-PdG is highly mutagenic and the formation of this DNA adduct can be facilitated in the presence of polyamines [3, 20]. Relevant polyamine concentrations are present in tissues that are in hyper-regenerative environments. Chronic alcohol consumption causes such an environment in the mucosa of the UADT [21], brought about by the high concentration of AD in the saliva [22]; thus leading to the generation of highly mutagenic Cr-PdG adducts in these tissues. This process may be related to carcinogenesis of the UADT, including the esophagus [3]. AD also binds to various proteins involved in DNA repair and DNA methylation and causes structural and functional alterations in these proteins [3, 23].

Reactive oxygen species (ROS) such as superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2) are generated by several enzyme systems, including cytochrome P450 2E1 (CYP2E1)-dependent microsomal monooxygenase. Chronic alcohol consumption in animals and humans induces the hepatic CYP2E1 enzyme at concentrations 10–20 times higher than those in subjects without chronic alcohol consumption [24, 25]. CYP2E1 induction by alcohol has also been confirmed in the gastrointestinal mucosa of animals [26]. CYP2E1 has a high rate of nicotinamide adenine dinucleotide phosphate, reduced

(NADPH) oxidase activity and produces a large amount of O_2^- and H_2O_2. Furthermore, chronic alcohol consumption also induces nitric oxide synthase and increases nitric oxide production, leading to the generation of highly reactive peroxynitrite ($ONOO^-$) [3, 27]. The ROS cause oxidative injury, inflammation, and lipid peroxidation [24]. Lipid peroxidation leads to the production of 4-hydroxynonenal, which reacts with DNA bases such as deoxyadenosine and deoxycytidine and forms exocyclic DNA adducts, which are highly mutagenic and induce a point mutation at the hotspot of the *p53* gene [3, 28]. Therefore, the oxidative stress caused by ROS is accepted as a critical pathophysiological mechanism in various human diseases, including cancer. In fact, malignant tumors often show increased levels of DNA base oxidation and mutations [29].

Ethanol itself may also stimulate carcinogenesis by inhibiting DNA methylation and by interacting with retinoid metabolism [3]. The methylation and the demethylation of genes are among the most important mechanisms for the regulation of gene transcription [30]. *S*-Adenosyl-L-methionine (SAM) is a universal methyl group donor and enzyme activator in methyl transfer reactions, and alcohol consumption inhibits SAM synthesis [31]. For example, the inhibition of SAM synthesis by alcohol leads to global hypomethylation of hepatic DNA but not of the *p53* gene, resulting in the upregulation of oncogenes and downregulation of tumor-suppressor genes [32]. Therefore, aberrant methyl transfer caused by the inhibition of SAM synthesis may be important for alcohol-mediated carcinogenesis [3]. Retinoic acid (RA) regulates the transcription of many genes that are important for cellular growth and differentiation by signaling through its nuclear receptors (RARs) [7]. Chronic alcohol consumption decreases RA concentrations in the liver by inducing CYP2E1 [33]. The disruption of RA metabolism and signaling may have an important role in carcinogenesis. For example, in the rat liver, the decrease in the RA level induced by alcohol results in the downregulation of RARs and the enhancement of AP-1 (c-Jun and c-Fos) expression, thus resulting in the hyperproliferation of hepatic cells and a decrease of apoptosis [3, 34].

Molecular mechanism of smoking-related carcinogenesis (Fig. 2)

Well-established carcinogens in cigarette smoke

Cigarette smoke is a cause of lung cancer, as well as being a cause of esophageal, oral, pharyngeal, laryngeal, pancreatic, and other cancers [5]. Cigarette smoke contains more than 60 carcinogens that have been evaluated by the IARC [4, 5]. Fifteen of these compounds are carcinogenic

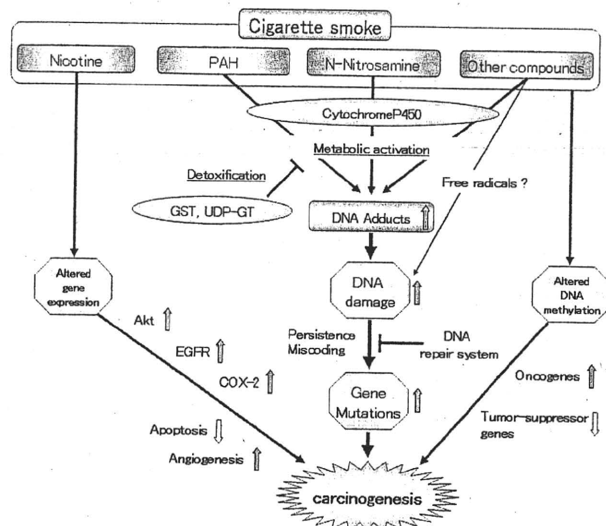

Fig. 2 Schematic presentation of compounds in cigarette smoke and their roles in carcinogenesis. *PAH* polycyclic aromatic hydrocarbons, *GST* glutathione-*S*-transferases, *UDP-GT* uridine diphosphate–glucuronosyl transferases, *EGFR* epidermal growth factor receptor, *COX-2* cyclooxygenase-2

in humans, with polycyclic aromatic hydrocarbons (PAHs) and *N*-nitrosamines being the most important carcinogens in cigarette smoke. There are strong links between these carcinogens and various types of smoking-induced cancers [35]. The mechanisms of their actions are believed to be the induction of DNA adducts, gene methylation and mutation, and chromosomal translocation in target organs [5, 7].

Benzo[*a*]pyrene (BaP) is one of the 10 PAH compounds listed by the IARC as carcinogens [4]. It has powerful carcinogenic activity and is considered to be carcinogenic to humans [36]. PAHs are usually locally acting carcinogens, and they also induce various kinds of cancer depending on the route of administration [5]. Although a causal link has been established between PAHs and cancer in skin, lung, and bladder cancers, evidence linking individual PAHs to ESCC is based only on ecological studies and is therefore circumstantial [37]. Evaluating the association of PAHs with ESCC has proven difficult, partly because there are no valid and reliable markers of long-term exposure to PAHs that can be used in epidemiological studies [37].

N-Nitrosamines also cause various cancers in several animal models [37]. The important *N*-nitrosamines in cigarette smoke are *N*-nitrosamines 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and *N'*-nitrosonornicotine (NNN). The tobacco-specific NNK is a potent lung carcinogen in animals and also induces pancreatic and nasal cavity tumors [38]. NNN is the most prevalent *N*-nitrosamine carcinogen in cigarette smoke, which causes tumors of the esophagus in rats [5, 39, 40].

Aromatic amines, formaldehyde, volatile hydrocarbons, organic compounds, metals, and other compounds contained in cigarette smoke are listed as carcinogens in humans by the IARC (reviewed by Hecht [5]). Cigarette smoke contains free radicals and induces oxidative damage [41]. Freshly generated cigarette smoke contains large amounts of nitric oxide and other unstable oxidants [42]. However, the role of oxidative damage as a cause of specific tobacco-induced cancers remains unclear [35].

General mechanisms of smoking-induced carcinogenesis

The major established pathway of carcinogenesis by cigarette smoke is the formation of covalent bonds between the carcinogens in smoke and DNA, which produces DNA adducts, resulting in permanent mutations in critical genes such as oncogenes and tumor-suppressor genes in somatic cells [5].

Most of the cigarette smoke carcinogens are oxygenated by cytochrome P450 enzymes and are converted to a form that is highly soluble in water [43]. However, some of the intermediates are quite reactive with DNA, resulting in the formation of DNA adducts [43, 44], which are central to the carcinogenic process [45]. This process is known as the metabolic activation of carcinogens [35]. The balance between the metabolic activation of carcinogens and detoxification by various enzymes, including glutathione-*S*-transferases [46] and uridine diphosphate (UDP)-glucuronosyl transferases [47], varies among individuals and is likely to affect cancer susceptibility. The levels of DNA adducts in the lung and other tissues are higher in smokers than in nonsmokers, and some data have demonstrated links between higher adduct levels and a higher probability of cancer development [6].

DNA adducts can be eliminated in normal cells by elaborate DNA repair systems [48]. For example, adducts of PAHs are repaired by nucleotide excision repair, and miscoding in methylated base O^6-methylguanine is repaired by a direct repair system with O^6-methylguanine DNA methyltransferase. DNA adducts persist if these repair systems are insufficient or overwhelmed by the amount of DNA damage. Mutations may arise during DNA replication if persisting DNA adducts are bypassed incorrectly by DNA polymerase, leading to dysregulation of normal cell growth and apoptosis, genomic instability, and a higher probability of cancer development [48, 49].

DNA adducts induced by different carcinogens may have significantly different mutational properties. Therefore, it is useful to identify the link between DNA damage and specific mutations in tumor cells in order to elucidate the role that environmental elements play in carcinogenesis in humans [35]. The available data indicate that many DNA adducts associated with cigarette smoke exposure may frequently produce G-to-T transversions [42]. For example, the mutational spectrum of the *p53* tumor-suppressor gene in lung cancer cells is similar to the mutation patterns induced in vitro by PAH metabolites [35, 50, 51]. The major adduct of BaP produces a G-to-T transversion [52] and the frequency of the G-to-T transversion is significantly higher in smokers than that in nonsmokers [35]. Methylated CpG dinucleotides are the preferred sites for G-to-T transversion, and the striking sequence specificity of benzo[*a*]pyrene-7,8-diol-9,10-epoxide (BPDE) for producing G-to-T transversion hotspots at methylated CpG sequences is similar to the distribution of G-to-T transversion hotspots in smoking-associated lung tumors [35, 51, 53].

Other possible mechanisms of smoking-induced carcinogenesis

There are other pathways in which carcinogens in cigarette smoke cause cancers. Nicotine, the main known addictive agent in cigarette smoke, may be at least partially involved in the initiation, promotion, and even progression of tumors [54, 55]. Nicotine modulates the phenotype of normal airway epithelial cells by rapidly activating Akt, a serine/threonine kinase, leading to decreased apoptosis and increased angiogenesis [56, 57]. Moreover, cigarette smoke activates the epidermal growth factor receptor (EGFR) tyrosine kinase in oral epithelial cells that then stimulates cyclooxygenase-2 (COX-2) [58]. This leads to the inhibition of apoptosis, promotion of angiogenesis, modulation of inflammation and immune function, and increased tumor cell invasiveness [59]. Epigenetic changes, such as the methylation of CpG islands, may therefore be another mechanism of smoking-induced carcinogenesis [60].

Synergistic effects of smoking and alcohol in carcinogenesis (Fig. 3)

Epidemiological data have suggested that alcohol interacts synergistically with cigarette smoke in the development of ESCC [61]. Alcohol is metabolized to AD locally in the oral cavity by the ADH of microbes in the normal oral flora. Heavy alcohol drinking, chronic smoking, and the poor oral hygiene frequently observed in drinkers and smokers modify the oral flora to contain a larger abundance of aerobic bacteria and yeasts which are highly capable of generating AD from ethanol [3, 62]. Furthermore, the ALDH enzyme in the oral mucosa in smokers is inhibited by microbial changes in the oral cavity due to smoking, resulting in a significant deposition of AD in the saliva [63]. Therefore, AD may link drinking alcohol, smoking, and poor oral health to ESCC [37].

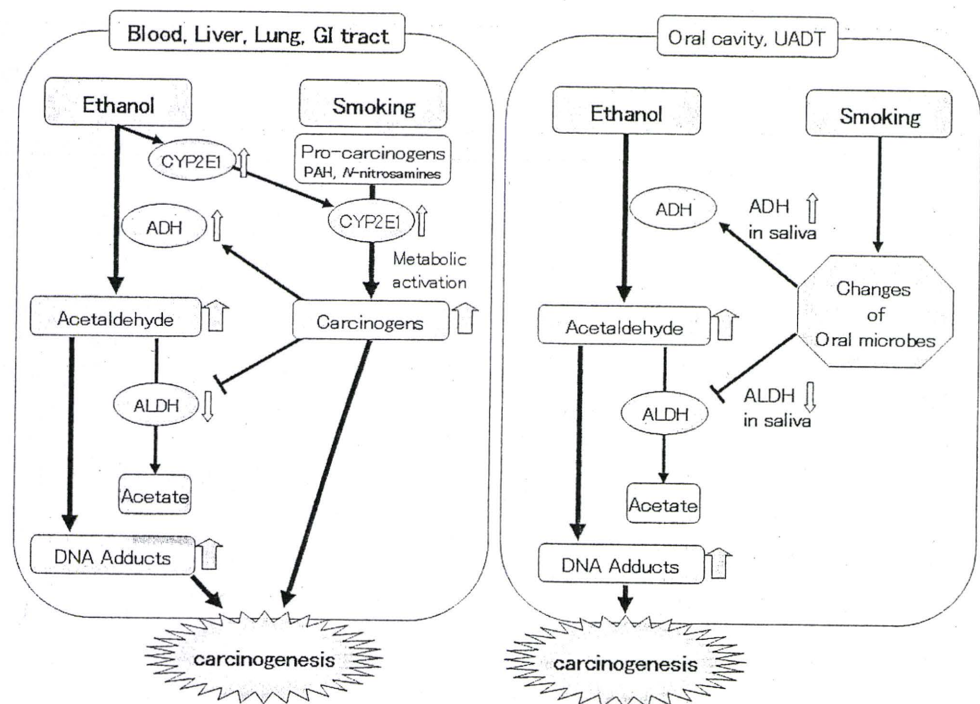

Fig. 3 Synergistic effects of smoking and alcohol in carcinogenesis. *GI* gastrointestinal, *UADT* upper aerodigestive tract, *ADH* alcohol dehydrogenase, *CYP2E1* cytochrome P450 2E1, *ALDH* aldehyde dehydrogenase

Also, chronic alcohol consumption induces cytochrome P450 enzymes in the liver and the gastrointestinal mucosa [24–26], possibly leading to acceleration of the metabolic activation of cigarette smoke-related procarcinogens to active carcinogens [35]. Furthermore, there is also evidence of inhibition of the ALDH enzyme by smoking, which leads to less efficient AD metabolism and, consequently, to higher AD concentrations in the UADTs of smokers [64]; as well, BaP increases the ADH level in bronchial epithelial cells (our data). All of these data suggest that AD derived from both ethanol and tobacco appears to act in the UADT as a local carcinogen in a synergistic way [65].

Molecular alterations in esophageal squamous cell carcinoma:review with a special focus on cigarette smoking and alcohol consumption

Numerous molecular alterations associated with the genesis of ESCC have been reported. These include alterations in cell-cycle regulation, growth factors and their receptors, and DNA repair systems. Such alterations in ESCC will be reviewed here, paying special attention to cigarette smoking and chronic alcohol consumption.

p53

p53 is a tumor-suppressor gene and its primary function is to maintain human genetic stability and DNA repair capacity [66]. The function of the *p53* gene is lost mainly by gene mutations, as well as by various other factors, including overexpression of the murine double minute gene 2 (*MDM2*); this causes acceleration of p53 degradation [67]) or inactivation of $p14^{ARF}$ [this protein suppresses MDM2 activity], leading to inhibition of cell-cycle arrest, DNA repair, and the subsequent apoptosis [68].

p53 is one of the first tumor-suppressor genes that has been shown to have undergone frequent point mutations in primary ESCC and ESCC cell lines [66]. The point mutations in this gene occur even at an early stage of ESCC and correlate with tumor progression [69], thus suggesting an important role of this abnormality in esophageal carcinogenesis. The reported frequencies of *p53* gene mutations vary from 17% to 84%, possibly because of differences in the analytical methods used [70]. Egashira et al. [70] investigated the frequency of mutation of this gene by very elaborate direct DNA sequencing and demonstrated that 47.4% of the patients with ESCC had a *p53* gene mutation. The prognostic value of *p53* gene mutations in ESCC is controversial.

The mutational spectrum of the *p53* gene in lung cancers is consistent with the mutation patterns induced by certain PAHs such as BaP in cigarette smoke [35, 50, 51]. The major adduct of BaP produces a G-to-T transversion [52], and 40%–50% of *p53* gene mutations in Japanese patients with ESCC are predominantly the transversion of G to T [70, 71]; these findings also suggest that cigarette smoke might be related to esophageal carcinogenesis. However, Pfeifer et al. [35] have noted that it is difficult to identify the unambiguous molecular signature of tobacco carcinogens in the *p53* mutational spectrum of esophageal cancer,

because the patterns of mutation are extremely heterogeneous. On the other hand, the main mutations caused by AD, the primary metabolite of alcohol, are G-to-A transitions [72]. Noori and Hou [73] demonstrated that the mutational spectrum induced in vitro by AD in the *HPRT* gene of human T lymphocytes was consistent with the predominance of G-to-A transitions and mutations at A:T base pairs in the *p53* gene in esophageal tumors. These data may indicate that various factors are related to esophageal carcinogenesis, including cigarette smoke and alcohol. Positive correlations between the ratios of heavy alcohol drinkers and cigarette smokers and a high accumulation of p53 protein, related to its gene mutations [74], have been demonstrated in ESCC [75, 76].

Multiple ESCCs frequently occur in individual patients [77]. Ito et al. [78] demonstrated that *p53* mutation profiling of multiple ESCCs was quite heterogeneous not only in the presence/absence of mutations but also in the mutational patterns if they exist. The finding of different *p53* gene mutations among multiple ESCCs suggested evidence of field carcinogenesis in the human esophagus. Furthermore, this finding may reflect the condition that the esophagus is exposed to a wide variety of carcinogens.

p21

The $p21^{WAF1/CIP1}$ gene, a cyclin-dependent kinase inhibitor (CDKI) induced by p53, mediates G1 arrest after DNA damage [79]. Although mutations or deletions in this gene are rarely reported in human cancers, polymorphisms of this gene may play some roles in esophageal carcinogenesis [80]. p53-dependent expression of p21 is observed in ESCC, while the lack of an absolute correlation between abnormal p53 protein expression and p21 protein expression suggests that p53-independent expression of p21 protein might also occur in ESCC [81]. The direct relationship between *p21* and carcinogens in cigarette smoke and alcohol has so far only seldom been studied.

$p16^{INK4a}$ and $p14^{ARF}$

p16 protein inhibits CDK 4 and 6 that bind to cyclin D1 and downregulate the pRb pathway which blocks cell-cycle progression from the G1 to S phase [60]. Inactivation of the $p16^{INK4a}$ gene is a frequent event in human cancers, and is associated with a homozygous deletion, genetic mutation, or aberrant DNA methylation [60, 82]. Losses of the *p16* gene and the subsequent protein expression occur in the early stage of ESCC carcinogenesis, either by promoter methylation or by loss of heterozygosity [8, 9, 83]. Silencing of the *p16* gene by promoter methylation plays a role in smoking-related lung cancer [60]. The radionuclides in cigarette smoke may explain the phenomenon of *p16* inactivation by promoter methylation in smoking-associated lung tumors [84]. Although the contribution of cigarette smoke to the inactivation of the *p16* gene in ESCC remains to be elucidated, Ito et al. [85] have reported that the promoter methylation rate of $p16^{INK4a}$ was 76% and hypermethylation of this gene tended to occur more frequently in heavy drinkers and smokers.

The $p14^{ARF}$ gene is transcribed from the same locus as $p16^{INK4a}$ by alternative splicing, and the protein product interacts with MDM2 protein, thus resulting in the stabilization of p53 [86]. The $p14^{ARF}$ promoter is aberrantly methylated in 61% of patients with ESCC, leading to downregulation of the expression of this gene [85].

Cyclin D1

Cyclin D1 protein is involved in the p16-pRb pathway and induces pRb phosphorylation with CDK4/6, indicating its critical role in the progression of the cell cycle through the G1 to S phase [87]. Amplification or overexpression of this gene plays an essential role in human esophageal carcinogenesis [11]. A causal relationship between tobacco carcinogens and *cyclin D1* upregulation has been reported in lung cancer, oral cancer, and ESCC. Hu et al. [88] reported that cigarette smoke extract stimulated cell proliferation and increased the cyclin D1 protein level in a dose-dependent manner in a human ESCC cell line. A correlation between alcohol consumption and upregulation of *cyclin D1* expression was also observed in esophageal cancer [89].

EGFR, RA, and RARs

EGFR is a receptor tyrosine kinase and plays an important role in cell-cycle regulation and carcinogenesis. EGFR is overexpressed in 29%–92% of resected ESCC specimens [11, 90]. *EGFR* gene amplification is one of the mechanisms of its activation [91], which can be a marker for predicting lymph node metastasis and unfavorable prognosis [91, 92]. *EGFR* gene mutations in esophageal carcinoma are rare, but they do exist [93].

RA can suppress EGF-associated cell proliferation and EGFR expression by inhibiting EGFR-dependent ERK1/2 activation [94, 95]. Immortalized human bronchial epithelial cells are transformed by NNK, a tobacco carcinogen, with overexpression of *EGFR* and *cyclin D1*. Retinoid treatment prevents this transformation by downregulating *EGFR* and *cyclin D1* expression [94]. *EGFR* expression is also inhibited in esophageal cancer cells by the induction of RA and RAR-β_2. Furthermore, BPDE, a potent carcinogen in cigarette smoke, can suppress RAR-β_2 expression in murine lung cancer through methylation of the *RAR-β_2* gene promoter [96]. Xu's group similarly demonstrated, in immortalized esophageal epithelial cells and esophageal

cancer cells, that BPDE-induced methylation of the *RAR-β_2* gene promoter, thus leading to the loss of RAR-β_2 expression [7, 97, 98]. This induced the overexpression of EGFR, ERK1/2, AP-1, and COX-2 [7].

The induction of CYP2E1 by alcohol can enhance the degradation of RA. Consequently, RA levels in cells are reduced, resulting in the altered expression of different genes, such as the reduced expression of *RAR-β_2* and increased expression of *EGFR*, *ERK1/2*, *AP-1*, and *COX-2* [99].

COX-2

COX-2 is one of the two enzymes that catalyze the first step in the synthesis of prostaglandins (PGs) from arachidonic acid. Multiple lines of evidence suggest that COX-2 is associated with many of the critical steps in carcinogenesis and tumor progression. Zimmermann et al. [100] have demonstrated that COX-2 is expressed in the majority of ESCC tissues and that COX-2-derived PGs play an important role in the regulation of proliferation and apoptosis of esophageal cancer cell lines. Various animal and human esophageal tissues contain high levels of PGs in cancer [59]. The levels of COX-2 have been shown to increase in the oral mucosa of smokers in comparison to those in nonsmokers, and the activation of EGFR signaling contributes to the elevated levels of COX-2 [58]. Furthermore, nicotine enhances the migration and invasion of human ESCC cell lines, a process which is inhibited by nimesulide, a selective COX-2 inhibitor that decreases the protein level of COX-2 [55].

E-cadherin

E-cadherin belongs to the cadherin family of Ca^{2+}-dependent cell–cell adhesion molecules and is a key molecule in the suppression of the epithelial–mesenchymal transition (EMT) that occurs during the development and progression of cancers. Yoshino et al. investigated the correlation between tobacco smoking and EMT in a lung cancer cell line and found that BaP decreased the E-cadherin expression level and induced EMT [101, 102]. Furthermore, Davis et al. [103] showed that nicotine significantly reduced the expression of E-cadherin in cultured lung, breast, and pancreatic cancer cells, leading to EMT. The association of E-cadherin expression and smoking or alcohol consumption in ESCC remains to be elucidated.

BRCA1

Several studies have shown a frequent loss of heterozygosity in the region of the *BRCA1* gene locus in ESCC [104], suggesting that BRCA1 may be a candidate tumor-suppressor gene in esophageal cancer. The finding that BPDE can bind to the *BRCA1* gene after normal esophageal epithelial cells are treated with BPDE may therefore be an important phenomenon [105].

FHIT

The fragile histidine triad *(FHIT)* gene has been identified as a candidate tumor-suppressor gene localized at chromosome 3p14.2 [106]. Inactivation of *FHIT* occurs at an early stage in the development of ESCC [107] and methylation of the *FHIT* gene promoter is closely associated with transcriptional inactivation in ESCC [108], which is linked to cigarette smoking [109]. Nicotine induces methylation of the *FHIT* gene in human ESCC cell lines and attenuates Fhit protein in association with the increased expression of DNA methyltransferase 3a, which is implicated primarily in de-novo methylation [110]. Furthermore, an association of the loss of Fhit protein with alcohol consumption is also suggested in human ESCC [111].

DNA repair genes

There is no direct evidence to show a correlation between cigarette smoke or alcohol consumption and the impairment of DNA repair systems in ESCC. Several studies have indicated that abnormalities of DNA repair systems are uncommon in esophageal carcinogenesis [112]. On the other hand, Mimori et al. [113] have reported that microsatellite instability is significantly related to allelic loss in the *FHIT* region, but that mutS homologue 2 might be unrelated to progression or the oncogenic process in ESCC.

Conclusion

Despite recent advances in diagnostic and surgical techniques and multimodal treatments, esophageal cancer still remains one of the most aggressive and lethal diseases [114, 115]. Many types of epidemiological data have demonstrated that both cigarette smoking and alcohol consumption are the two major risk factors for the development of ESCC [61]. The aim of the present review was to summarize the current evidence for contributory mechanisms of alcohol- and smoking-induced carcinogenesis and to discuss the molecular mechanisms of esophageal carcinogenesis with special attention to these carcinogens. Although the most important goal in conquering ESCC is to prevent the development of this disastrous disease by enlightening the public about the risk of these carcinogens, it is equally important to clearly elucidate the underlying mechanisms of esophageal carcinogenesis. However, a comprehensive

understanding of the molecular mechanisms of esophageal carcinogenesis remains elusive. Therefore, greater effort is required to identify more genetic changes, as well as epigenetic changes such as the methylation and acetylation or deacetylation of histones and other important proteins which are observed in esophageal cancer [116, 117]. These mechanistic insights could be translated into practical approaches for the prevention and cure of alcohol- and smoking-induced esophageal cancer.

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特集 基礎から最新治療まで 最前線のリンパ浮腫ケア

リンパ浮腫のクリニカルパス

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はじめに

国内のリンパ浮腫標準的治療指針はまだ確立されていない。そのためリンパ浮腫患者への治療・ケアはまちまちで，放置されていることもしばしばである。

筆者は厚生労働省の班研究[注1)]で検討した標準的リンパ浮腫診療クリニカルパスをケアの指針として公開することで，リンパ浮腫治療の底上げが図れるものと考える。この標準リンパ浮腫診療クリニカルパスは，ここ数カ月以内に，国立がん研究センターのがん情報サービスHPに公開を予定している。

クリニカルパスの内容はリンパ浮腫の各病期と特殊な時期の診断・治療・処置についてであるが，これに沿った診療を行うことで，もれのない診療が行える内容とした。現在日本におけるがん治療後のリンパ浮腫治療は保存的治療が主流である。

がん治療後のリンパ浮腫保存的治療クリニカルパス(診療用)の検討手順

標準リンパ浮腫保存的治療クリニカルパス(診療用)の内容は，がん診療連携拠点病院もしくはそれに準ずる病院で行われるべき治療内容とし，リンパ浮腫診療を積極的に行っている8施設で検討した。研究メンバーを**表1**に示す。

注1)厚生労働科学研究費補助金(第3次対がん総合戦略研究事業)「患者・家族・国民に役立つ情報提供のためのがん情報データベースや医療機関データベースの構築に関する研究」〔平成19-21年度／主任研究者・若尾文彦(国立がん研究センター)〕の研究小班「がんクリニカルパスデータベース構築に関する研究」〔分担研究者・新海哲/河村進(四国がんセンター)〕でがん関連の標準クリニカルパスを検討している。現在7大がんとリンパ浮腫のパスを検討しており，作成されたパスは順次下記HPに公開している。
http://ganjoho.jp/professional/med_info/pass/index.html

リンパ浮腫保存的治療クリニカルパス(診療用)の適応基準と除外基準

リンパ浮腫保存的治療クリニカルパス(診療用)の適応基準と除外基準につき，以下に示す。

適応基準：腋窩，骨盤内，鼠径部のリンパ節郭清術もしくは，放射線治療を行った乳がん，婦人科がん，消化器がん，膀胱がん，前立腺がん，四肢の皮膚がん症例とリンパ節転移による浮腫，化学療法施行症例の浮腫

除外基準：蜂窩織炎などの急性炎症，うっ血性心不全，深部静脈血栓症急性期，重症虚血肢

①蜂窩織炎などの急性炎症がある場合には炎症を助長するため，②うっ血性心不全患者では患肢の圧迫療法を行うと心不全が悪化することがあるため，③深部静脈血栓急性期ではリンパドレナージ手技で血栓を遊離させ肺塞栓となる危険性があるため，また④重症虚血肢に圧迫療法を行うと患肢の壊死を来たす危険性があるため，それぞれ治療を控える必要がある。

リンパ浮腫保存的治療クリニカルパス(診療用)の項目設定

横軸に入院時の説明，病期0期(がん治療後予防期)，Ⅰ期，Ⅱ期早期，Ⅱ期晩期，Ⅲ期を，縦軸に症状，目標，指導説明，観察確認，処置治療，検査，活動・清潔・食事，受診時期と間隔を設定した。

1) 病期別の症状，ケア，観察項目など

クリニカルパス(**表2，3**)に病期別の症状，治療ケア，観察項目を記載した。症状の進行度によって複合的治療[注2]を中心としたケアのなかで圧迫療法の比重が高くなってくることに注目されたい。重要なのは術前からリンパ浮腫発症リスクの説明を行うこと，術後早期から発症予防のケアについて理解してもらうことである。観察項目にある周径計測の部位は各施設での設定でよいが，経時的な比較のために毎回同部位を測定する必要がある。例えば，上肢で腋窩，肘上10cm，肘下5cm，手関節，手背を，下肢で太ももの付け根，膝上10cm，膝下10cm，足関節，足背と決めて計測する。

注2)複合的治療とは
「複合的理学療法」に日常生活指導を加えた保存的治療方法のことで，「複合的理学療法」とはスキンケア，用手的リンパドレナージ，圧迫療法，圧迫下の運動療法の4本柱で行うリンパ浮腫の保存的治療法のことである。

究 ポイント！

表1 注1)の研究班の標準リンパ浮腫診療クリニカルパス検討ワークグループメンバー

施設	氏名
松尾クリニック	松尾汎
リムズ徳島クリニック	小川佳宏
廣田内科クリニック	廣田彰男
東京大学医学部附属病院 形成外科	光嶋勲
東海病院　下肢静脈瘤・リンパ浮腫・血管センター	平井正文
後藤学園附属リンパ浮腫治療研究所	佐藤佳代子
九州中央病院乳腺外科	北村薫
四国がんセンター　形成外科	河村進

表2 リンパ浮腫保存的治療クリニカルパス(診療用)

病期	入院時の説明	0期（がん治療後予防期）	Ⅰ期	Ⅱ期早期
症状		還流障害はあるがリンパ浮腫は顕在化していない	夕方になるとむくむ程度、患肢挙上で浮腫改善、部位により圧迫痕が残りやすくなる（圧迫痕は下肢に現れやすいが上肢では現れることが少ない）	安静臥床や患肢挙上でも浮腫改善しない 皮膚は硬くなるが圧迫痕は残る
目標	リンパ浮腫の病態(リスク）が説明ができる 予防のための日常生活の注意点が説明ができる ケアの方法が説明ができる 早期発見の方法が説明ができる	リンパ浮腫の病態(リスク）が説明ができる 予防のための日常生活の注意点が説明ができる セルフケアの方法が説明ができる 早期発見の方法が説明ができる	リンパ浮腫の病態が説明ができる 日常生活の注意点が理解でき実行できるように指導ができる セルフケアの方法が理解でき実行できるように指導ができる 進行をおさえ浮腫が改善できるように指導ができる	リンパ浮腫の病態が説明ができる 日常生活の注意点が理解でき実行できるように指導ができる セルフケアの方法が理解でき実行できるように指導ができる 進行をおさえ浮腫が改善できるように指導ができる 弾性包帯の施術と指導ができる
指導説明	リンパ浮腫指導管理料の算定要件にそった説明指導 ・リンパ浮腫の病因と病態 ・リンパ浮腫の治療方法の概要 ・セルフケアの重要性と局所へのリンパ液の停滞を予防及び改善するための具体的実施方法 ・生活上の具体的注意事項 ・感染症の発症等増悪時の対処方法	リンパ浮腫の病態の説明 複合的治療の主に下記について 日常生活上の注意点 スキンケア指導（浮腫の増悪と蜂窩織炎の予防） 早期発見の方法	リンパ浮腫の病態、病期の説明 複合的治療の主に下記について 日常生活上の注意点の説明 スキンケア指導（浮腫の増悪と蜂窩織炎誘発の予防） セルフリンパドレナージ指導 圧迫療法（弾性着衣）の説明 圧迫下の運動療法の説明 弾性着衣などの療養費申請方法(6ヶ月に一度は可能)	リンパ浮腫の病態、病期の説明 複合的治療の主に下記について 日常生活上の注意点の説明 スキンケア指導（浮腫の増悪と蜂窩織炎誘発の予防） セルフリンパドレナージ指導 圧迫療法（弾性着衣）の説明 圧迫下の運動療法の説明 弾性着衣などの療養費申請方法(6ヶ月に一度は可能)
観察確認	周径計測（左右）術前 術後 上肢(腋窩・上腕・前腕・手首・手部) 下肢（鼠径・大腿・下腿・足首・足部） 体重測定 患者の理解度の確認 指導管理料100点算定（入院中1回）	周径計測（左右）術前 退院時 上肢(腋窩・上腕・前腕・手首・手部) 下肢（鼠径・大腿・下腿・足首・足部） 浮腫の有無 体重測定 患者の理解度とセルフケアの実施状況の確認 ・入院時手術前説明の内容 皮膚を指腹で10秒間圧迫することによる圧迫痕の有無（左右の比較） 指導管理料100点算定（退院後1回）	周径計測（左右） 上肢（腋窩、上腕、前腕、手首、手部） 下肢（鼠径、大腿、下腿、足首、足部） 表在静脈の見えにくさの確認（健側との比較） 皮膚乾燥の有無 皮膚を指腹で10秒間圧迫することによる圧迫痕の有無（健側との比較） 皮膚がつまみあげにくい部位の確認 炎症症状の有無 体重測定 患者の理解度とセルフケアの実施状況の確認（2回目の受診以降） 指導管理料100点算定（退院後1回）	周径計測（左右） 上肢（腋窩、上腕、前腕、手首、手部） 下肢（鼠径、大腿、下腿、足首、足部） 表在静脈の見えにくさの確認（健側との比較） 皮膚乾燥の有無 皮膚を指腹で10秒間圧迫することによる圧迫痕の有無（健側との比較） 皮膚がつまみあげにくい部位の確認 炎症症状の有無 体重測定 患者の理解度とセルフケアの実施状況の確認（2回目の受診以降）
処置治療			複合的治療 患肢挙上 スキンケア セルフリンパドレナージ 弾性着衣の選定と着用指導（必要時） 圧迫下の運動療法（必要時）	複合的治療 患肢挙上 スキンケア 用手的リンパドレナージ （セルフ＋専門的な知識・技術を要する医療者による指導と施術を推奨。） 圧迫療法 ①弾性着衣の選定と着用指導 ②必要に応じて弾性包帯の施術と指導 （専門的な知識・技術を要する医療者による指導と施術を推奨。） 圧迫下の運動療法
薬物治療		リンパ浮腫単独に対する効果的な薬剤はない	リンパ浮腫単独に対する効果的な薬剤はない	リンパ浮腫単独に対する効果的な薬剤はない
検査	特になし	特になし	血液生化学一般検査／胸部エックス線／心電図／血管超音波：DVTや全身性浮腫との鑑別診断に実施する（必要に応じて実施する） 超音波／CT検査／MRI検査：リンパ浮腫の確定診断（必要に応じて実施する） リンパシンチグラフィ／蛍光リンパ管造影：考慮されることもある	血液生化学一般検査／胸部エックス線／心電図／血管超音波：DVTや全身性浮腫との鑑別診断に実施する（必要に応じて実施する） 超音波／CT検査／MRI検査：リンパ浮腫の確定診断（必要に応じて実施する） リンパシンチグラフィ／蛍光リンパ管造影：考慮されることもある
活動 清潔 食事	（日常生活上の注意点に則っていれば）、特に制限なし	（日常生活上の注意点に則っていれば）、特に制限なし	（日常生活上の注意点に則っていれば）、特に制限なし	（日常生活上の注意点に則っていれば）、特に制限なし
受診時期と間隔	症状出現時には早めの受診	症状出現時には早めの受診	セルフケアを習得するまでは頻回(必要により入院）に、習得後は3－6か月毎（弾性着衣の療養費支給も考慮） 症状変化に応じて適宜増減	セルフケアを習得するまでは頻回(必要により入院）に、習得後は3－6か月毎（弾性着衣の療養費支給も考慮） 症状変化に応じて適宜増減

適応基準：腋窩、骨盤内、鼠径部のリンパ節郭清術もしくは、放射線治療を行った乳がん、婦人科がん、消化器がん、膀胱がん、前立腺がん、四肢の皮膚がん症例 とリンパ節転移による浮腫、化学療法施行症例の浮腫

除外基準：蜂窩織炎などの急性炎症、うっ血性心不全、深部静脈血栓症急性期、重症虚血肢

このパスはリンパ浮腫診療の専門施設で使用することを前提とする

複合的治療とは複合的理学療法を中心とする保存的治療のことである
複合的理学療法とはスキンケア、用手的リンパドレナージ、圧迫療法、圧迫下の運動療法の４本柱で行うリンパ浮腫の保存的治療法のことである

注釈

1. 0期でのセルフリンパドレナージはハイリスク症例で行うこともあるが、根拠がないため原則行わない
2. リンパ浮腫指導管理料100点（入院中1回、外来受診時に1回算定できる）
3. 周径計測の部位は各施設で設定するが毎回同部位を測定する
4. 検査と処置はあくまでも推奨である
5. 受診間隔はあくまでも目安であり施設により異なる。悪化時は適宜短縮する
6. 弾性包帯・弾性着衣は個別にそして部分的に素材の選定・圧迫方法の工夫などを要する

表3 リンパ浮腫保存的治療クリニカルパス(診療用)

Ⅱ期晩期	Ⅲ期
安静臥床や患肢挙上でも浮腫改善しない 皮膚が硬くなり圧迫痕が残りにくくなる。	皮膚が硬くなり圧迫痕は残らなくなる 乳頭腫、リンパ小疱、リンパ漏、象皮症などの合併症が出現する
リンパ浮腫の病態が説明ができる 日常生活の注意点が理解でき実行できるように説明ができる セルフケアの方法が理解でき実行できるように指導ができる 進行をおさえ浮腫が改善できるように指導ができる 弾性包帯の施術と指導ができる	リンパ浮腫の病態が説明ができる 日常生活の注意点が理解でき実行できるように説明ができる セルフケアの方法が理解でき実行できるように指導ができる 進行をおさえ浮腫が改善できるように指導ができる 弾性包帯の施術と指導ができる
リンパ浮腫の病態、病期の説明 複合的治療の主に下記について 日常生活上の注意点の説明 スキンケア指導（浮腫の増悪と蜂窩織炎誘発の予防） セルフリンパドレナージ指導 圧迫療法（弾性着衣）の説明 圧迫下の運動療法の説明 弾性着衣などの療養費申請方法(6ヶ月に一度は可能)	リンパ浮腫の病態、病期の説明 複合的治療の主に下記について 日常生活上の注意点の説明 スキンケア指導（浮腫の増悪と蜂窩織炎誘発の予防） セルフリンパドレナージ指導 圧迫療法（弾性着衣）の説明、 圧迫下の運動療法の説明 弾性着衣などの療養費申請方法(6ヶ月に一度は可能) 合併症の治療の説明
周径計測（左右） 上肢（腋窩、上腕、前腕、手首、手部） 下肢（鼠径、大腿、下腿、足首、足部） 表在静脈の見えにくさの確認（健側との比較） 皮膚乾燥の有無 皮膚を指腹で10秒間圧迫することによる圧迫痕の有無（健側との比較） 皮膚がつまみあげにくい部位の確認 炎症症状の有無 皮膚硬化の有無 体重測定 患者の理解度とセルフケアの実施状況の確認（2回目の受診以降）	周径計測（左右） 上肢（腋窩、上腕、前腕、手首、手部） 下肢（鼠径、大腿、下腿、足首、足部） 表在静脈の見えにくさの確認（健側との比較） 皮膚乾燥の有無 皮膚を指腹で10秒間圧迫することによる圧迫痕の有無（健側との比較） 皮膚がつまみあげにくい部位の確認 炎症症状の有無 皮膚硬化の有無 体重測定 合併症（乳頭腫、リンパ小疱 、リンパ漏）の有無 患者の理解度とセルフケアの実施状況の確認（2回目の受診以降）
複合的治療 患肢挙上 スキンケア 用手的リンパドレナージ （セルフ＋専門的な知識・技術を要する医療者による指導と施術を推奨。） 圧迫療法 ①必要に応じて弾性包帯の施術と指導 ②弾性着衣の選定と着用指導 （専門的な知識・技術を要する医療者による指導と施術を推奨。） 圧迫下の運動療法 入院治療を推奨（専門的な知識・技術を要する医療者による指導と施術を推奨。）	複合的治療 患肢挙上 スキンケア（象皮症には皮膚軟化剤を使用）尿素製剤など？ 用手的リンパドレナージ （セルフ＋専門的な知識・技術を要する医療者による指導と施術を推奨。） 圧迫療法 ①必要に応じて弾性包帯の施術と指導 ②弾性着衣の選定と着用指導 （専門的な知識・技術を要する医療者による指導と施術を推奨。） 圧迫下の運動療法 合併症の治療 入院治療を推奨（専門的な知識・技術を要する医療者による指導と施術を推奨。）
リンパ浮腫単独に対する効果的な薬剤はない	リンパ浮腫単独に対する効果的な薬剤はない
血液生化学一般検査 胸部エックス線 心電図 血管超音波 超音波 ― DVTや全身性浮腫との鑑別診断に実施する（必要に応じて実施する） CT検査 MRＩ検査 ― リンパ浮腫の確定診断（必要に応じて実施する） リンパシンチグラフィ 蛍光リンパ管造影 ― 考慮されることもある	血液生化学一般検査 胸部エックス線 心電図 血管超音波 ― DVTや全身性浮腫との鑑別診断に実施する（必要に応じて実施する） 超音波 CT検査 MRＩ検査 ― リンパ浮腫の確定診断（必要に応じて実施する） リンパシンチグラフィ 蛍光リンパ管造影 ― 考慮されることもある
（日常生活上の注意点に則っていれば）、特に制限なし	（日常生活上の注意点に則っていれば）、特に制限なし
セルフケアを習得するまでは頻回(必要により入院）に、習得後は3−6か月毎（弾性着衣の療養費支給も考慮） 症状変化に応じて適宜増減	セルフケアを習得するまでは頻回(必要により入院）に、習得後は3−6か月毎（弾性着衣の療養費支給も考慮） 症状変化に応じて適宜増減

※説明内容の詳細については患者用説明パンフレットを参照する

2）リンパ浮腫外来への受診間隔

外来受診は，安定期にあるリンパ浮腫症例は初診から2回目の受診までの間隔を約1カ月とし，進行がないかマッサージが適切に行えているかなどをチェックする。その後は症状によって3カ月後，6カ月後の受診とする。セルフチェックで症状悪化がある場合には早めの受診を指示する。

①入院時の説明

2008年4月1日の診療報酬改定でリンパ浮腫指導管理料100点が認められた。

算定要件は，リンパ浮腫の病因と病態，リンパ浮腫の治療方法の概要，セルフケアの重要性と局所へのリンパ液の停滞を予防及び改善するための具体的実施方法，生活上の具体的注意事項，感染症の発症等増悪時の対処方法を説明指導することである。

この期に重要なのは術前の周径計測結果の記録である。周径計測はリンパ浮腫が発症した場合の比較のために全病期で必要であり，定期的な測定結果は改善や悪化の度合いの評価に用いることができる。

②0期(がん治療後予防期)

還流障害はあるがリンパ浮腫の症状は顕在化していない時期。

この期ではリンパ浮腫の早期発見の方法を説明することが重要であり，予防のためのスキンケアと日常生活の注意点の指導が主となる。この時期の用手的セルフリンパドレナージは原則行わない。

2010年4月1日から外来でも退院後1回に限りリンパ浮腫指導管理料100点が追加算定できるようになった。

③I期

浮腫は患肢の安静・挙上で改善するが，圧迫痕が残りやすくなる時期。

この期の治療はスキンケアとセルフリンパドレナージ指導が主となり，弾性着衣(圧迫スリーブ，圧迫ストッキング)による圧迫療法は必要時にのみ行う。弾性着衣の購入指示を行った場合には，療養費の申請で購入代金の7割が支給されるのでその申請方法を説明する。リンパ浮腫の確定診断には超音波，CT,MRI検査が必要に応じて行われる。

④II期早期

安静臥床や患肢挙上でも浮腫が改善しない。皮膚は硬くなるが圧迫痕は残る時期。

専門的な知識・技術を有する医療者による用手的セルフリンパドレナージの指導と施術が推奨され，弾性着衣の使用が中心となる。必要に応じて包帯法(弾性包帯)の指導と施術を行う。

⑤II期晩期

安静臥床や患肢挙上でも浮腫が改善しない。皮膚が硬くなり圧迫痕が残りにくくなる時期。

専門的な知識・技術を有する医療者による包帯法(弾性包帯)の指導と施術が中心となり，入院治療が推奨される。

⑥III期

浮腫が硬化し圧迫痕が残らない。乳頭腫，リンパ小疱，リンパ漏，象皮症などが合併する時期。

専門的な知識・技術を有する医療者による包帯法(弾性包帯)の指導と施術が中心となり，合併症治療を含めた入院治療が推奨される。

特殊な時期のリンパ浮腫保存的治療クリニカルパス(診療用)

進行・再発・転移に伴う高度のリンパ浮腫，緩和医療対象(終末)期のリンパ浮腫，蜂巣炎・蜂窩織炎を伴うリンパ浮腫の3つの時期で内容を検討した(**表4**)。

①進行・再発・転移に伴う高度のリンパ浮腫

皮膚浸潤，リンパ節転移により急激に悪化した浮腫

- スキンケアと軽い圧迫療法(チューブ包帯，伸縮包帯)が中心となる。
- 用手的リンパドレナージについては原疾患治療医と相

表4 特殊な時期のリンパ浮腫保存的治療クリニカルパス(診療用)

	進行・再発・転移に伴う高度のリンパ浮腫
症状	皮膚浸潤、リンパ節転移による急激な皮膚の硬化、発赤などの増悪
目標	リンパ浮腫の病態が説明ができる 日常生活の注意点が理解でき実行できるように説明ができる セルフケアの方法が理解でき実行できるように指導ができる 進行をおさえ浮腫が改善できるように指導ができる ADL QOLの維持・改善を図ることができる
指導 説明	リンパ浮腫の病態、病期の説明 複合的治療の主に下記について 日常生活上の注意点の説明 スキンケア指導(浮腫の増悪と蜂窩織炎誘発の予防) リンパドレナージ指導 圧迫療法の説明 心理的・社会的サポート
観察 確認	皮膚乾燥の有無 表在静脈の見えにくさの確認(健側との比較) 周径計測(左右) 上肢(腋窩、上腕、前腕、手首、手部) 下肢(鼠径、大腿、下腿、足首、足部) 炎症症状の有無 皮膚硬化の有無 リンパ漏の有無 体重測定
処置 治療	複合的治療 スキンケア 患肢挙上 用手的リンパドレナージ 圧迫(チューブ包帯または伸縮性包帯で軽く) 圧迫療法と運動療法を中心とし、用手的リンパドレナージについては原疾患治療医と相談のうえ行う
薬物治療	リンパ浮腫単独に対する効果的な薬剤はない (全身性浮腫を合併する場合はその原因に応じた薬剤を使用する)
検査	血液生化学一般検査 胸部エックス線 心電図 血管超音波 超音波 (以上、DVTや全身性浮腫との鑑別診断に実施する(必要に応じて実施する)) CT検査 MRI検査 (以上、リンパ浮腫の確定診断(必要に応じて実施する)) リンパシンチグラフィ 蛍光リンパ管造影 (以上、考慮されることもある)
活動 清潔 食事	(日常生活上の注意点に則っていれば)、特に制限なし

	緩和医療対象(終末)期のリンパ浮腫
症状	がん終末期患者のリンパ浮腫　全身性浮腫を合併して皮膚が脆弱となる
目標	安楽を保つケアができる ADL QOLの維持・改善を図ることができる
指導 説明	複合的治療の主に下記について スキンケア指導(浮腫と蜂窩織炎誘発の予防) 心理的・社会的サポート
観察 確認	炎症症状の有無 皮膚乾燥の有無 皮膚の脆弱性の有無 全身性浮腫の有無 リンパ漏の有無 リンパ小疱の有無
処置 治療	本人の希望を優先 複合的治療 スキンケア 患肢挙上 タッチング 圧迫(チューブ包帯または伸縮性包帯で軽く) 圧迫療法を中心とするが用手的リンパドレナージについては主治医と患者に相談のうえ行う
薬物治療	リンパ浮腫単独に対する効果的な薬剤はない (全身性浮腫を合併する場合はその原因に応じた薬剤を使用する。)
検査	必要に応じて全身性浮腫との鑑別を行なう 疼痛のなどの原因検索
活動 清潔 食事	(日常生活上の注意点に則っていれば)、特に制限なし

	蜂巣炎・蜂窩織炎を伴うリンパ浮腫
症状	皮膚に急性炎症症状がある
目標	蜂窩織炎の病態が説明できる 治療の必要性が説明できる 炎症症状が改善する治療・ケアができる
指導 説明	リンパ浮腫にともなう蜂窩織炎の説明 スキンケア指導(浮腫と蜂窩織炎誘発の予防) 安静冷却の必要性の説明 用手的リンパドレナージと圧迫療法の再開タイミングの説明
観察 確認	全身の発熱の有無 皮膚の発赤、腫脹、疼痛、熱感の有無 皮膚乾燥の有無 周径計測(左右) 上肢(腋窩、上腕、前腕、手首、手部) 下肢(鼠径、大腿、下腿、足首、足部) 皮膚硬化の有無 体重測定 全身性浮腫の有無 皮膚の脆弱性の有無
処置 治療	複合的治療 スキンケア 患肢の安静挙上 局所の冷却(冷やしすぎない工夫を) 圧迫・用手的リンパドレナージの休止
薬物治療	抗生物質と消炎鎮痛剤の投与
検査	血液検査(CBC CRP)
活動 清潔 食事	炎症が治まるまで安静、患肢挙上。発熱が治まるまでは入浴をひかえる。

談のうえ行う。
・深部静脈閉塞を伴い急速に浮腫が進行することがあるので鑑別を要する。

②緩和医療対象時期のリンパ浮腫

がん終末期患者のリンパ浮腫。全身性浮腫を合併して皮膚が脆弱となる。
・患者の希望を優先して苦痛になることは行わないのが原則である。
・スキンケアとタッチング程度の軽いリンパドレナージと軽い圧迫治療(チューブ包帯，伸縮包帯)が中心となる。
・用手的リンパドレナージについては原疾患治療医と相談の上行う。
・心不全などを合併することが多いため治療には注意を要する。

③蜂巣炎・蜂窩織炎

リンパ浮腫の部位に生じた急性炎症
炎症が治まるまでは安静，患肢挙上，局所の冷却を行い，抗生物質，消炎鎮痛剤を投与する。局所性の熱感が消失し発赤が軽減すれば，リンパドレナージと圧迫療法を開始する。全身発熱を伴う場合は原則入院治療とする。

まとめ

リンパ浮腫診療を専門とする医師もリンパドレナージセラピストも少ない現状では，担当看護師がリンパ浮腫患者のボディイメージの変化を受けとめ情緒的支援とリンパ浮腫ケアの説明指導にかかわる必要がある。標準的リンパ浮腫診療クリニカルパスの公開により，適切なリンパ浮腫診療が行える医療者と医療施設の増加を期待する。

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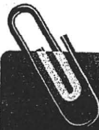
日本看護協会看護研修学校　認定看護師教育課程の平成23年度入学試験

＊今年度から試験日程が変わりますのでご注意ください！
＊平成22年6月，協会ニュースや日本看護協会HPにて平成23年入学試験の案内開始
(日本看護協会 認定看護師教育 http://www.nurse.or.jp/nursing/education/nintei/index.cgi)
■入学試験日程と会場：
日程：平成22年9月14日㈫，15日㈬
会場：日本看護協会看護研修学校(東京都清瀬市梅園1-2-3)
■募集学科と定員：
救急看護，集中ケア，皮膚・排泄，感染管理，糖尿病看護，小児救急看護，認知症看護
各学科　定員30名
■願書受付期間：
平成22年7月12日㈪～8月6日㈮
■問合せ先：
社団法人日本看護協会看護研修学校教務係
〒204-0024　東京都清瀬市梅園1-2-3
TEL：042-492-7464　FAX：042-492-8653



症例 case report

原発性十二指腸癌を含む同時性3重複癌（多発大腸・胃・十二指腸）の1例*

原　康之　臼田昌広　中野達也
平野拓司　望月　泉　小野貞英**

はじめに

近年，術前・術後の各種診断技術の向上や高齢化に伴う第2癌の発生などにより重複癌の報告は増加傾向にある．特に原発性十二指腸癌を含む3重複癌以上の報告はまれである．今回われわれは，原発性十二指腸癌を含む同時性3重複癌（多発大腸・胃・十二指腸）の1例を経験したので，文献的考察を加え報告する．

症　　例

症　例　53歳，男性

主　訴：左側腹部痛

家族歴：父，肺炎で死亡．母親，大動脈瘤破裂で死亡．その他，家族・親戚に悪性疾患の既往はない．

既往歴：5年前から高血圧で内服中であった．

現病歴：2005年7月初旬に左側腹部痛を主訴に当院を受診し一時帰宅した．その後軟便と食欲低下が出現したため8月再診した．Hb 10.7g/dlと貧血を認め，血清腫瘍マーカーのCEAが7.7ng/mlと上昇していた．精査・加療目的で入院となった．

入院時所見：身長170cm，体重62kgであった．眼瞼結膜に軽度貧血を認めた．左上腹部に腫瘤を触知した．表在リンパ節の腫脹は認めなかった．

入院時検査所見：WBC 9,280/μl，CRP 10.58 mg/dlと炎症所見を認めた．Hb 10.7g/dl，Ht 33.2％と軽度貧血も認めた．腫瘍マーカーはCEA 7.7ng/ml，CA19-9 15.9ng/mlと上昇していた．

腹部CT所見：左腎腹側に不均一に造影される径6cm大の腫瘍を認めた（図1）．

注腸造影所見：下行結腸に腫瘍による完全閉塞所見を，S状結腸に辺縁が比較的明瞭な隆起性病変を認めた（図2）．

上部消化管内視鏡所見：胃体上部後壁にⅡc病変（図3a）を十二指腸下行脚に2型腫瘍（図3b）を認め，いずれもGroup Ⅴであった．

下部消化管内視鏡所見：下行結腸に巨大腫瘍（図4a）を認め，口側腸管の評価はできなかった．S状結腸に径4cm大の1型腫瘍（図4b）を認めた．いずれも生検でGroup 4であった．

以上の検査所見から胃癌・十二指腸癌・下行結腸癌・S状結腸癌の同時性重複癌と診断した．

第1回手術所見：下行結腸に12×10cmの巨大腫瘍を認め，一部は腹壁に浸潤していた．胃・十二指腸・S状結腸にも腫瘍を触知した．それぞれの病変を一期的に切除することとし，胃部分切除・幽門輪温存膵頭十二指腸切除・結腸左半切除・S状結腸部分切除を施行した．

第1回切除標本所見：下行結腸は2型，105×98mm，中分化型腺癌でpSI，ly1，v1，n(－)．S状結腸はIp type，29×28mm，高分化型腺癌でpSM，ly1，v1，n(－)．胃は0～Ⅱc，12×9mm，中分化型管状腺癌でsm2，ly1，v1，n(－)．十二指腸は2型，34×30mm，中分化型腺癌，ss，ly1，v2，n(－)であった．病理組織学的には，腫瘍間の距離・各々の分化度の違い・腫瘍の進展様式・明らかなリンパ節転移がないことなどから，それぞれが原発の腫瘍であると診断された．

キーワード：原発性十二指腸癌，同時性重複癌，多発大腸癌

* A case of synchronous triple cancer including primary duodenal cancer

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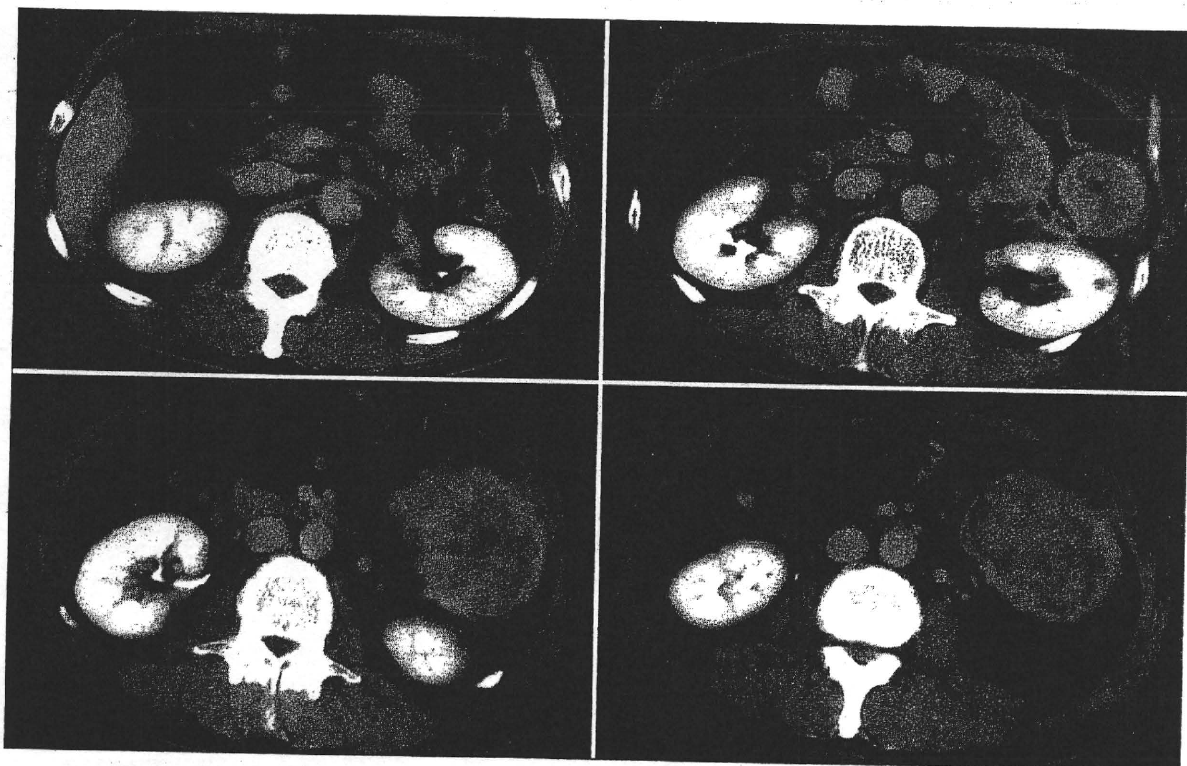
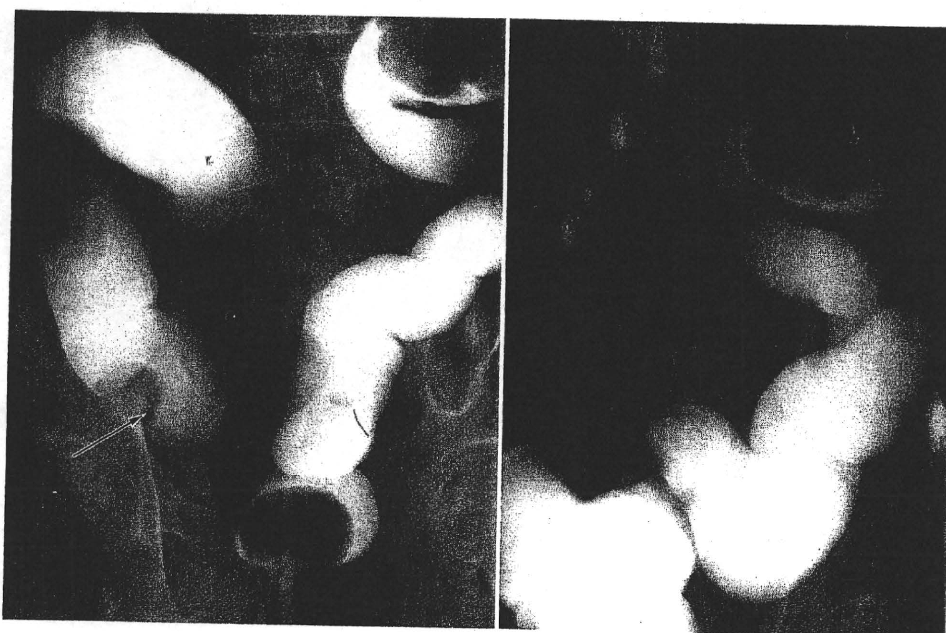


図1. 腹部CT
左腎腹側に不均一に造影される径6cm大の腫瘍を認める.



a. S状結腸　　b. 下行結腸

図2. 注腸造影像
下行結腸に腫瘍による完全閉塞所見を，S状結腸に辺縁が比較的明瞭な隆起性病変(矢印)を認める.

術後膵空腸吻合部の縫合不全・創感染を合併したが軽快し術後73日目に退院した. 経過観察中の2006年6月に血便が出現したため，精査目的で当院に入院した. 大腸内視鏡で肝彎曲部に1/2周性の2型腫瘍を認め，生検でGroup V(高分化型腺癌)が検出された. 同部位の結腸癌の診断で手術の方針となった.

第2回手術所見：前回手術の影響で広範囲に癒