Comprehensive Integration of Treatments and Therapies for Esophageal Cancer

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Abstract: Esophageal cancer is one of the most deadly malignant tumors worldwide, with high mortality and few therapeutic options. It ranks as the eighth most prevalent cancer globally and the sixth largest factor of common cancer-related death. Epigenetics is of great interest in the adenocarcinoma stage of its development and undergoing intense investigation as a field for potential translation towards both research and therapy of esophageal cancer. This focus highlights a methylation of RNA and an epigenetic alteration of N6-methyladenosine (m6A). Another significant mechanism associated with esophageal cancer is DNA methylation. Esophageal cancer frequently results in abnormal DNA methylation events, such as hypomethylation of oncogenes and hypermethylation of tumor suppressor genes. The impact of nutrition on esophageal cancer both before and after therapy has been studied, much like the previously described treatment approaches. However, the most cutting-edge approach to cancer treatment is the use of nanomaterials, which offer therapeutic chemicals or target-specific therapy.

1 INTRODUCTION

Esophageal cancer is among the most aggressive and lethal cancer withhigh mortality and poor treatment option globally. Globally it is the 8th most common cancer and the 6th common cause of cancer deaths. In terms of results, the 20% 5- year survival of esophagal cancer was very similar with the results in the same years reported by the American National Cancer Institute; however, the reported 5years survival of esophagal cancer varied from 5% to 47%. The two histological subtypes of esophageal cancer (EC)—esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC)—have been shown to differ in their molecular and aetiological processes. Use of tobacco, alcohol, obesity, gastroesophageal reflux disease (GERD), and certain foods and beverages, like processed meats and hot beverages, are risk factors (Liang et al. 2023). The outlook for esophageal cancer remains poor, with current methods of detection and efficient systemic approaches both being unavailable, and a five-year survival rate at less than 20% still remains. This highlights the need for new approaches to enhance early diagnosis of disease, treatment response, and patient prognostication. But when one of the most common forms and cause of cancer-related death in the world—esophageal cancer—epigenetics is being studied in research and therapy. Among these epigenetic modifications, RNA N6-methyladenosine (m6A) has attracted great interest. N6-methyladenosine (m6A) is the most plentiful known internal modification found in eukaryotic mRNA and plays roles in RNA metabolism such as splicing, stability, translation, and degradation process. Accumulating evidence indicates that m6A modification deregulation is linked with various cancers, including esophageal cancer, and is crucial in tumorigenesis and various processes of cancer progression, including tumor growth, metastasis, and resistance to anticancer therapy. Moreover, new therapeutic targets are utilizing m6A-modifying enzymes—methyltransferases (writers), demethylases (erasers), and binding proteins (readers) that may be involved in regulating m6A-mediated gene expression to prevent cancer initiation and development (Teng et al. 2022).

Esophageal cancer is also closely associated with DNA methylation, yet another key epigenetic phenomenon. Abnormal DNA methylation, including hypermethylation of tumor suppressor

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genes and hypomethylation of oncogenes, is prevalent in esophageal cancer. In most cases of tumorgenesis, this process can inactivate some key genes that are responsible for cell cycle regulation, apoptosis, and DNA damage repair (Chen et al. 2018). The therapies targeting this epigenetic aberration in esophageal are forming as a candidate for therapy such as reverse aberrant methylation patterns like DNA methyltransferase inhibitors. Apart from the therapeutic approaches mentioned previously, the significance of nutrition in the prevention and treatment of esophageal cancer has also been described. Not just folates vitamin B12, well known that molecules speak to some kind of epigenetic processing, like DNA methylation therefore as RNA methylation (Meng et al. 2023). For instance, folate is an essential precursor for SAM, the main methyl-acceptor in the methylation pathway. Nutritional interventions can reverse the normal epigenetic regulation circuit by changing the availability of methyl donors and other bioactive compounds that prevent cancer (Miller & Bozeman 2022). The types of diets or food types that support a healthy gut microbiome, reduce inflammation, and starve the potential cancer-feeders in our gut microbiome still need to be investigated. Nanomaterials are able to successfully deliver therapeutic agents in a deliberate and targeted manner, which indicates a new direction in the innovative generation of cancer therapy. Nanomaterials (nanoparticles or nanocarriers) can be engineered to facilitate the target-specific delivery of drugs, siRNAs, or epigenetic modulators to tumor cells, resulting in lower systemic toxicity and increased treatment efficacy (Wang et al. 2018).

2 FUNDAMENTAL MECHANISMS OF RNA N6-METHYLADENOSINE AND EFFICACY IN SUPPRESSING ESOPHAGEAL CANCER

In eukaryotes, N6-methyladenosine (m6A) is an extensively researched internal RNA alteration. One of the most prevalent post-transcriptional changes is adenosine methylation. Site-specific methylation (m6A) is structured by adding methyl groups (CH3) to the RNA subunits, generally at the nitrogen-6position of movements of adenosine, which alters mRNAs slightly. m6A participates in oncogenetic signals to promote tumorgenesis, metastasis, and drug resistance. The "writer" complex that mediates m6A modification is made up of the methyltransferase complex METTL3, METTL14, WTAP, and other associated proteins. While the METTL3 subunit acts as a catalytic base, METTL14 acts mainly to stabilize METTL3 and enhance activity. By digitally demethylating the m6A residues, "eraser" proteins such as FTO (fat mass and obesity-associated protein) and ALKBH5 (alkB homolog 5) eliminate m6A marks. The recognition of m6A by particular binding proteins, referred to as "readers," which modify the fates of m6A-modified RNAs, is what drives the biological activities of m6A in cells. Specifically, m6A-modified RNA is recognized and bound by the YTH domain-containing family proteins (YTHDF1/2/3 and YTHDC1/2). An immune cell infiltration (ICI) risk model was presented in a work by Nie et al. that involved mapping the m6A alteration of single-cell RNA sequencing of esophageal squamous cell carcinoma (ESCC) H9699 cells (Nie et al. 2023). In this work, Nie et al. uncovered the distinct m6A modification patterns in esophageal squamous cell carcinoma (ESCC) cells and conducted a thorough investigation into the relationship between tumor heterogeneity and tumor micro-environmental variables and m6A modification patterns. Additionally, this method developed a predictive risk model that uses immune-related genes linked to m6A to forecast the degree of immune infiltration and patient prognosis risk. The model showed the substantial effects of m6A modifications on immune cell infiltration and prognostic signature for the progression of ESCC (Nie et al. 2023). These observations not only shed light on the molecular mechanisms of RNA methylation regulation involved in ESCC pathogenesis but also imply that restoring the m6A modification levels of methyltransferase may provide a therapeutic strategy to hinder tumor immune evasion and enhance clinical outcome in ESCC patients.

Liang et al. gives another example from the field in Cancer Letters, which reported the original research "Methyltransferase-like 3 facilitates esophageal cancer stem cell properties by upregulating patched homolog-1 via N6-methyladenosine methylation" (Liang et al. 2023). This study provides a thorough analysis of the RNA methyltransferase METTL3 in driving cancer stem cell (CSC) properties in esophageal carcinoma. In their work published in the American Journal of Physiology-Cell Physiology on September 1, 2023,

a team of researchers revealed that METTL3-mediated N6-methyladenosine (m6A) airway modification upregulated Patched homolog-1 (PTCH1), a critical member of the Hedgehog signaling pathway, that could lead to induction of stemness and tumorigenicity (He et al. 2023). Through additional characterization, molecular and cellular studies support that METTL3 binds PTCH1 mRNA and promotes its expression by enhancing m6A methylation and activation of the Hedgehog signaling pathway. This mechanism promotes esophageal cancer cell self-renewal and proliferation and induces chemoresistance. Depletion of METTL3 in experimental studies decreases cancer stem cell (CSC) features and tumor growth, whereas overexpression of METTL3 is sufficient in enhancing these features. These findings demonstrate METTL3's carcinogenic role in fostering stemness and imply that METTL3 targeting is a viable therapeutic approach for blocking carcinogenic signaling in esophageal cancer.

3 APPLICATION OF GENE METHYLATION AND ITS RELEVANCE TO ESOPHAGEAL CANCER TREATMENT

Gene methylation has been regarded as a key regulator of gene expression and one of the major types of epigenetic modification. It can also amplify or silence the transcription of individual genes. Aberrant DNA methylation, particularly global hypomethylation and locus-specific hypermethylation, is a feature of tumorigenesis. It contributes to genome instability and transcriptional repression of tumor suppressor genes and transcriptional activation of oncogenic pathways in esophageal cancer. Notably, promoter hypermethylation of genes involved in cell cycle regulation, apoptosis, and DNA repair, such as CDKN2A, APC, and MLH1, are significantly associated with transcriptional silencing, which is presumed to promote the malignant transformation and progression of esophageal squamous cell carcinoma (ESCC). Methylation profiling has both a diagnostic and a therapeutic role in esophageal cancer management. Methylation signatures hold great potential as biomarkers for early detection and risk stratification. HoAXA9 and PCDHGA12 were established as hypermethylation-sensitive assays for diagnosis in ESCC.

In order to shed light on the part that aberrant DNA methylation plays in esophageal squamous cell carcinoma (ESCC), Xi et al. recently published a paper in Signal Transduction and Targeted Therapy (Xi et al. 2022). It is done by conducting a thorough multi-omics analysis that makes it easier to find clinically significant biomarkers. The authors described a distinct epigenetic landscape of ESCC using an integrated approach that included transcriptomic data, whole-genome bisulfite sequencing (WGBS; 42 samples), genome-wide DNA methylation profiling of 425 ESCC patients and 54 normal controls, and clinical follow-up information. They discovered 2,735 hypermethylated and hypomethylated (3,879) genomic regions when comparing tumors versus the normal tissue, and they varied throughout, primarily in the promoter regions. These changes were associated with transcriptional repression of tumor suppressor genes, including HOXA9 and PCDHGA12, which disrupted the Wnt/β-catenin and MAPK pathways to drive tumor progression. Clinically, the article presented a 12−CpG methylation−site detection panel that differentiated ESCC from adjacent normal tissues at high diagnostic powers (AUC = 0.957−0.985). This panel was validated on independent patient sets and in liquid biopsy samples, suggesting its possible benefit for non-invasive diagnostic strategies. A prognostic model was then constructed based on 5-methylation markers (HOXA9, PCDHGA12, TFPI2, ZNF671, and SIM2) that divided patients into high- and low-risk groups. Patients that were classified as high-risk had significantly worse overall survival than those classified as low-risk (median overall survival: 23 VS 64 months, $p < 0.001$). Functional assays confirmed that demethylating agents like 5-aza-2'-deoxycytidine reactivated silenced genes (e.g, HOXA9) and inhibited ESCC cell proliferation. Methylation-mediated immune evasion strategies in hypomethylated regions were found to be associated with immunosuppressive microenvironments. Thus, the present study provides the first comprehensive epigenomic map of ESCC tumorigenesis and identifies numerous candidate biomarkers for early diagnosis, prognosis, and pharmacotherapy, highlighting the translational relevance of targeting DNA methylation to enhance clinical efficacy in ESCC.

Using integrated transcriptomic and clinical data from the TCGA esophageal carcinoma cohort (184 tumors, 11 normal tissues), Xu et al conducted systematic analyses of 21 m6A regulators (writers — e.g., METTL3, WTAP; erasers— e.g., FTO, ALKBH5; readers— e.g., YTHDF2, HNRNPC). Differential expression analysis revealed that 14 regulators were significantly dysregulated in tumors compared to normal tissues ($p < 0.05$). Six overall survival (OS)-related regulators (METTL14, YTHDF2, YTHDF1, HNRNPA2B1, FTO, and ZC3H13) were found using univariate Cox regression analysis. These were then further filtered using the multivariate Cox model to create a four-gene prognostic signature (YTHDF1, YTHDF2, HNRNPA2B1, and METTL14). Patients were divided into high- and low-risk groups according to the median risk scores, which were generated by weighting the coefficients. High-risk patients had a considerably shorter OS than low-risk patients (median OS: 18.6 vs. 47.1 months, $p < 0.001$), and the signature's prognostic performance was acceptable (1-year AUC = 0.72; 3-year AUC=0.69). The multivariate analysis demonstrated that the risk score was an independent prognostic factor of overall survival (OS) (HR = 1.26, 95% CI: 1.12–1.43, $p < 0.001$), which was still retained when adjusted for clinical covariates (age, stage, grade). Functional enrichment analyses suggested strong correlation of high-risk scores with tumorigenesis-associated pathways, including Wnt/β-catenin signaling, RNA splicing, and metabolic reprogramming. The prognostic significance of the signature was also validated independently in another cohort (GSE53625, n=119) (log-rank p=0.002) (Xi et al. 2022).

4 APPROACHES TO NUTRITIONAL THERAPY FOR ESOPHAGEAL CANCER PATIENTS

Esophageal carcinoma is a malignant tumor with high morbidity and significant nutrition high-impact complications generated, thus requiring unique therapeutic strategies that consider the complex causal relationship between the progression of the disease, complications of treatments and nutrient metabolic disorders. Jordan et al. underscore the importance of therapies based on nutrition and omitting foods that cause allergic reactions. This was underscored in a landmark study published in 2018 entitled Nutritional therapy for Patients with Esophageal Cancer, which advocated that the impact of malnutrition on treatment efficacy and clinical outcomes is significant. They based this conclusion on a synthesis of data from clinical trials and observational studies demonstrating that early and systematic use of nutrition therapy, using enteral feeding protocols and dietary adjustments, is associated with reduced postoperative complication rates, better tolerance of chemotherapy, and improved survival rates. For instance, by reviewing literature, they showed that post-esophagectomy infectious complications were reduced by 22% with perioperative enteral nutrition (EN) as compared to parenteral modalities and emphasized the critical role of gut integrity as a lung-immunological mediator of gastrointestinal (GI) and immune toxicities. Furthermore, the authors reduce our attention to the DE-factochemistry of malnutrition to the recognition of the therapeutic relevance of organized digital nutritional evaluation, demonstrating that patients whose treatment was guided by the Patient-Generated Subjective Global Assessment (PG-SGA) had 80% fewer unplanned readmissions. This observation supports the predictive value of proactive nutritional surveillance. This review seeks to distill the evidence supporting the various aforementioned pathophysiological components along with those presented by Dr. Bultman and Dr. Marshall to offer a broad paradigm of nutritional therapy based on the work of Jordan et al. This framework indicates a need for multidisciplinary collaborations, a need for tailored nutrition interventions, and a need for cancer-targeting agent incursion to concomitantly address the multimodal needs of esophageal cancer patients (Jordan et al. 2018).

It is with this in mind that esophageal cancer represents the rare neoplasm that is potentially curable, but likely not unless such is accompanied by the presence of rigorous compliance to an oncologic dietetic regimen; indeed, in the context of other esophageal approaches targeting improved nutrition (i.e., PEG), the emergence of regimented nutritional protocols in the milieu of CCRT to esophageal carcinogenic is required to counterbalance the synergistically deleterious impact of dysphagia, metabolic stress, and treatment toxicity. Qiu et al. carried out a randomized controlled trial (RCT) to assess the feasibility and effectiveness of whole-course nutrition management (WCNM), a multimodal

method incorporating proactive assessment, tailored dietary planning, and therapeutic monitoring in 120 patients with locally advanced esophageal squamous cell carcinoma (Qiu et al. 2020). A total of 120 participants were randomized to either the control group, which received conventional care (n = 60), or the Whole-Course Nutrition Management (WCNM) group (n = 60). Anthropometric (BMI, mid-arm circumference), biochemical (serum albumin, prealbumin), and Patient-Generated Subjective Global Assessment (PG-SGA) parameters are used to determine the baseline nutritional status. Moreover, surpluses and deficiencies in body composition were evaluated using BIA (Bioelectrical Impedance Analysis). During the formal treatment phase, caloric and protein needs were assessed by means of indirect calorimetry, with targets set at 25–30 kcal/kg/day and 1.5 g of protein/kg/day, respectively. High-energy oral nutritional supplements (ONS) were used to optimize daily intake, and modified-texture diets (e.g., puréed or liquid formulations for patients with dysphagia) and intermittent enteral nutrition (EN) via nasogastric tubes were prescribed for those whose oral intake compliance was less than 60% (67% of patients).

Weekly evaluations were performed during the intensive treatment cycles to monitor weight changes and gastrointestinal toxicity (CT CAE v4.0), and metabolic parameters. Issues like anorexia, mucositis, or dehydration were handled adaptively. In actual fact, by far the most thorough assessment, the WCNM group had much greater maintenance of lean body mass (LBM) (+3.2 kg and 2.1 kg; p=0.01) and serum albumin levels (35.2 g/L and 30.1 g/L; p=0.003) at the end of CCRT. They also achieved more completed CCRT cycles (81.7% vs. 63.3%; p=0.02) and experienced less grade 3 esophagitis (18.3% vs. 35.0%; p=0.04). In a 12-month follow-up, the authors observed better PFS in the WCNM group (HR: 0.62; 95% CI: 0.41-0.93; p=0.02), and this was explained by immunological resilience and less treatment suspension. Motivated by conclusions, the WCNM framework utilizes anticipatory nutritional support to alleviate the catabolic cascades driven by CCRT. Preservation of mucosal integrity alongside reductions in cytokine-driven muscle wasting is achieved by the establishment of WCNM-derived anabolic substrates (e.g., branched-chain amino acids, omega-3 fatty acids) and oxidative stress. In addition, earlier initiation of EN maintains the gut-associated lymphoid tissue (SALT) activity and decreases bacterial translocation and associated systemic inflammation. The findings underscore the need for nutrition therapy to be incorporated into oncology care pathways. This paradigm shift in the management of nutrition from reactive management to proactive behavioral interventions—such as real-time adaptation to toxicities—corresponds with emerging evidence that optimum nutrition influences therapeutic efficacy and survivorship in esophageal cancer. WCNM's Multidisciplinary Approach in both Oncologic Workflows and Nutritional Interventions Future clinical protocols must adopt the interdisciplinary framework established by WCNM, integrating dietitian-led clinical interventions within oncologic workflows to expand the standards of care delivery (Qiu et al. 2020).

5 TARGETED NANOMATERIALS FOR ESOPHAGEAL CANCER THERAPY

Nanomaterials are utilized to deliver therapeutic agents for the treatment of esophageal cancer (EC), achieving efficiency against distinct biological barriers using high surface-area-to-volume ratios, tunable surface chemistries, and responsive behaviors, particularly for the size range of 1–100 nm. Both passive and active targeting mechanisms are at the core of their design. Passive targeting utilizes the leaky structure of tumor vasculature by facilitating the specific accumulation of nanoparticles (NPS) in tumor tissues via the enhanced permeation and retention (EPR) effect. In this method, NPS are covered with ligands, which can include chemicals, peptides, and antibodies that can bind to certain biomarkers on the surface of esophageal tumor cells such as EGFR, HER2, and FR. Xiao et al. also emphasize that dual-targeting delivery systems, which combine both strategies, achieve greatly improved drug bioavailability and cellular uptake and elicit much lower toxicity to healthy tissues. This is a critical breakthrough for the treatment of esophageal cancer tumor tissues that are anatomically complex and heterogeneous (Xiao et al. 2023). Nanomaterial platforms for efficient electrocution therapy in Xiao's study include: **(1) Lipid-Based Nanoparticles:** Liposomes are a natural delivery system providing a basophilic environment for hydrophobic chemotherapeutics

(e.g. paclitaxel) and nucleic acids. Solid lipid nanoparticles (SLNs) are the next generation of lipid nanoparticles. Xiao et al. highlight how functionalization of these nanoparticles with anti-CD44 antibodies allows for targeting of cancer stem cells in esophagus cancer, which leads to improved tumor penetration and lower rate of recurrence (Xiao et al. 2023). **(2) Polymeric Nanoparticulates:** LPGA and chitosan-based nanoparticles are used for controlled release of drugs and to provide adherence to the mucosa. The latter property increases the lumen residence time and thus improves localized delivery of agents like 5-fluorouracil, as noted by Xiao et al. **(3) Inorganic Nanomaterials:** Inorganic nanoparticles such as gold nanoparticles (AuNPs) and iron oxide nanoparticles (IONP) are commonly used as both diagnostic and therapeutic modalities. For example, AuNPs enable photothermal therapy (PTT) upon exposure to near-infrared (NIR) light, while IONPs can be used for MRI-guided hyperthermia, as demonstrated in preclinical studies of esophageal cancer. **(4) Stimuli-Responsive Nanosystems:** Xiao et al. discuss the emergence of nanoparticles that trigger payload release in response to cues derived from the tumor microenvironment (e.g., acidic pH, matrix metalloproteinases [MMPs]) or external stimuli (e.g., light, magnetic fields). It enables the targeted release mechanism, decreasing off-target toxicity (Xiao et al. 2023).

To overcome these obstacles, the advent of nanomedicine has proposed a novel paradigm combining diagnostic with therapeutic functions. Li et al. suggested that they will discuss the recent advances in nanomedicine to combat hepatocellular carcinoma (HCC) and delineate the biophysicochemical mechanisms by which innovative materials can allow precision, reduce off-target effects, and the capacity to overcome biological barriers (Li et al. 2022). Efficacy of Nanomedicine in Esophageal Cancer (EC) Nanomedicine delivery systems mainly consist of targeted delivery mechanisms, which can be divided into passive targeting and active targeting delivery systems. Passive targeting is based on the enhanced permeability and retention (EPR) effect, which allows nanoparticles (NPs) to selectively accumulate in solid tumors due to leaky vasculature and dysfunctional lymphatic drainage. Active targeting increases specificity via functionalization of NPs with ligands including antibodies, peptides, or aptamers that interact with EC-related markers such as epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), and Claudin 18.2. Li et al. report that dual-targeted platforms driving bioaccumulation maximize cellular uptake by exploiting both EPR-dependent aggregation and ligand-receptor (LR) interactions (Li et al. 2022). By way of example, anti-EGFR-conjugated NPs have exhibited deep penetration into tumors in preclinical models and inhibited metastatic spread while sparing normal esophagus tissues from injury. Simultaneously, multifunctional nanoplatforms for EC diagnosis and therapy are developed and improved. Polymeric nanoparticles are suitable materials for the controlled delivery of chemotherapeutics (e.g., paclitaxel or 5-fluorouracil) or poly (lactic-co-glycolic acid) (PLGA), whereas inorganic nanomaterials (e.g., gold or iron oxide nanoparticles) are used for both imaging and therapy. Nanogold is a theranostic that can be employed in PTT processes using NIR irradiation; its strong photoacoustic imaging capability makes it also an excellent contrast agent.

pH-sensitive covered doxorubicin-loaded MSNs have also been demonstrated to not only improve solubilization but also release the payload once within the acidic TME, thus helping reduce the effect of drug resistance. Such advances reflect the continued transition to personalized, image-guided treatments that are more rational given the molecular heterogeneity of esophageal cancer (EC). But major translational barriers persist. Li et al. established the overwhelming extracellular matrix, hypoxic TMEs, and heterogeneity of receptor expression in patients as critical barriers to leading to nanomedicine clinical efficacy (Li et al. 2022). In addition, the need for extensive preclinical validation due to concerns of long-term biocompatibility, scalability of synthesis, and regulatory issues further complicates translation to clinical applications. To overcome such limitations, they suggest utilizing patient-derived xenograft (PDX) models and organoid-based drug testing platforms to better mimic the pathophysiology of human EC. According to a study published in 2017, the ZD1-D/siCTLA4 targeted local delivery of cisplatin, a small molecule anti-cancer drug, can inhibit immune checkpoint pathways and break immune tolerance with immune checkpoint inhibitors, which is presumably achieved by this combinatorial way, namely, co-delivery of chemotherapeutics with immune checkpoint inhibitors or small interference RNA (siRNA) against oncogenic pathways to overcome the resistance mechanism and improve the efficiency of

the anti-tumor therapy (Li et al. 2022). Nanomedicine, therefore, glimmers a new dawn in esophageal cancer (EC) intervention, where diagnostic accuracy and targeted delivery would gradually be replaced by multifunctionality at the nanoscale to address the bottlenecks in conventional therapies. Li et al. point out future work will have to be interdisciplinary in order to inform best practices in material design, safety profile validation, and regulatory strategy. Next-generation nanoplatforms can revolutionize EC therapy due to their capability to harness advances in biomarker discovery and nanotechnology, which lead to improved early detection, better therapeutic precision, and higher survival rates (Li et al. 2022).

6 CONCLUSION

Esophageal cancer (EC) is a highly aggressive malignancy with high morbidity and mortality rates. It is still an important global health problem because of its rapid evolution and frequent late diagnosis. Standard of (SoCs) for early dependent stage and progressed EC based on recent molecular information, therapeutic medicines approved for different signs of cancer, and supportive consideration measures at that point have radically. Over can totally change the computational administration of EC. But these strategies may not be enough to conquer all the obstacles presented by this disease. RNA N6-methyladenosine (m6A) modifications have emerged as important modulators of the gene expression alterations that arise during EC suppression.

More specifically, m6A regulates post-transcriptional gene expression in RNA stability, splicing, translation, and so on. Of note, both the methyltransferase METTL3 and the demethylase are implicated in EC dysfunction, thereby presenting competitive therapeutic avenues through which tumor suppressor pathways can be re-established. Additionally, abnormal DNA methylation—particularly hypermethylation of tumor suppressor gene promoters such as CDKN2A and APC—can be utilized not only as a biomarker for early detection but also as a target for demethylating agents (e.g., azacitidine). While m6A modulation can enhance tumor sensitivity to epigenetic therapies by repressing target gene expression, off-target effects and limited mechanistic understanding of these therapeutic strategies remain significant barriers to their clinical implementation. Epithelial-mesenchymal transition (EMT) is a hallmark of malignancy. Such functionalized nanoparticles allow targeted delivery of chemotherapeutic drugs (e.g., paclitaxel) or siRNA directly to a tumor via ligand-receptor interactions (e.g., Incorporating this strategy improves drug bioavailability, reduces systemic toxicity, and circumvents multidrug resistance. Synergy can also be achieved through the application of photothermal and redox-responsive nanomaterials. However, the scalability of this approach, its biocompatibility, and its long-term safety need to be thoroughly assessed through clinical evaluation. Nutritional therapy, including high-protein oral supplements, enteral feeding in gastrostomy tubes, and optimization of micronutrients (e.g., zinc, selenium), alleviates cachexia and restores immune function. In particular, a tailored dietary plan (i.e., developed according to a patient's goals and treatment phases) ensures adequate postoperative recovery and increases chemoradiation resistance. However, differences in socioeconomic status and gastrointestinal complications may restrict adherence to the diet. Managing esophageal cancer (EC) remains a major clinical challenge, despite numerous advances. Nonspecific symptoms and lack of effective biomarkers make early detection challenging. Biologically, tumor heterogeneity is a challenge in incorporating standardized therapies, which highlights the need for biomarkers for patient stratification. Epigenetic and RNA-modulating therapies can be non-specific and activate off-target genes. The translation of nanomaterials is also bottlenecked by regulatory barriers and manufacturing complexities. Second, nutritional support should be integrated into oncological care, which can often be neglected in resource-poor settings due to the need for multidisciplinary collaboration.

A singular multidisciplinary approach—blending molecular biology, nanotechnology, and integrative holistic supportive care—is paramount. Liquid biopsies and AI-informed diagnostics might enable earlier detection. Combination therapies, such as m6A inhibitors + immunotherapy, are investigated in clinical trials and have the potential for synergistic efficacies. Finally, despite the promising perspectives opened up by the convergence of molecular biology, nanotechnology, and nutritional science towards achieving a new field in the context of a better understanding of EC, several biological and systemic issues that can compromise the treatment outcome (survival and quality of life) for patients all over the

world remain to be solved before this new treatment modality can be introduced.

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