International Journal of Emerging Trends in Pharmacy and Medicine
Vol. 01 (02), Apr - Jun 2025, pp. 12-23.
Online ISSN: 3107-4103
©IGRF Pvt. Ltd.

Advanced Diagnostic and Treatment Approaches for Esophageal Cancer

FAHEEMA BEGUM A

Department of Pharmacology, Faculty of Pharmacy, Dr. MGR Educational and Research Institute Poonamallee High Road, Velappanchavadi, Chennai, Tamil Nadu, India - 600077
faheema.a2004@gmail.com

SHADAP KHAN A

Department of Pharmacology, Faculty of Pharmacy, Dr. MGR Educational and Research Institute Poonamallee High Road, Velappanchavadi, Chennai, Tamil Nadu, India - 600077

NAVEEN BALA

Department of Pharmacology, Faculty of Pharmacy, Dr. MGR Educational and Research Institute Poonamallee High Road, Velappanchavadi, Chennai, Tamil Nadu, India - 600077
naveenbalaksr@gmail.com

ANKUL SINGH S*

Department of Pharmacology, Faculty of Pharmacy, Dr. MGR Educational and Research Institute Poonamallee High Road, Velappanchavadi, Chennai, Tamil Nadu, India - 600077
sankulsingh57@gmail.com

Abstract

The greatest survival rate for esophageal carcinoma is less than 20% or around five years, according to various surveys. Worldwide, esophageal cancer ranks sixth in terms of cancer-related death. Additionally, it ranks as the tenth most prevalent cancer type. The main things that can put you at risk for endocrinopathy include things like drinking and smoking. Adenocarcinoma (EAC) and squamous cell carcinoma (ESCC) are the two main histological subtypes of esophageal cancer. The epidemiological and clinical features of each are distinct. The ESCC is more dangerous than the EAC, and men are more likely to get EC than women. It is a highly aggressive and deadly disease. Several tests can be performed for the diagnosis of Esophageal cancer, the tests include barium swallow study, Biopsy, CT scan, MRI Scan, Bronchoscopy, PET Scan, Thoracoscopy, Etc. After the diagnosis of EC, the patients are treated according to their stages. The most common treatment options may include the following: Surgery (Esophagogastrostomy, Laparoscopic surgery, Gastrostomy, Esophagectomy), Medical procedures (Chemoradiation therapy, Radiation therapy, Laser therapy, Electrocoagulation), Chemotherapy. Other than this, newer treatment options like Targeted drug therapy and Immunotherapy are playing an emerging role in the treatment of EC by improving the quality of life. Nowadays, Artificial Intelligence (AI) is significantly contributing to improving EC's

*Corresponding Author.

dismal outlook. Different strategies based on artificial intelligence (AI), including chromo endoscopy, Confocal laser endomicroscopy (CLE), and clinicopathologic, and in order to diagnose and treat EC genetic factors have been created. The advanced diagnostic and treatment approaches for EC are discussed briefly in this article.

Keywords: Adenocarcinoma, AI Tools, Diagnosis, Esophageal Cancer, Immunotherapy, Nivolumab, Pembrolizumab, Squamous Cell Carcinoma, Survival Rate, Targeted Drug Therapy, Treatment.

1. INTRODUCTION

The rarest and potentially fatal type of cancer that can arise in the esophagus is esophageal cancer, according to Arnal (2015). The two most prevalent forms of esophageal cancer in humans, according to Sheikh et al. (2023), are esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC).

- **Esophageal Adenocarcinoma (EAC)** - This kind of cancer develops in the distal esophageal lining's glandular cells that produce mucus (Sheikh et al., 2023). It often produces fluids like mucus in the bottom portion of the esophagus, which is close to the stomach. One known cause of Barrett's esophagus is GERD, which stands for gastroesophageal reflux disease. The great majority of esophageal cancer cases are adenocarcinoma (Sheikh et al., 2023).
- **Esophageal Squamous Cell Carcinoma (ESCC)** - The delicate, flat esophageal lining is a potential site for squamous cell carcinoma to grow. The top two-thirds of the esophagus, which is situated near the throat, are usually affected (Sheikh et al., 2023). Using tobacco products and alcoholic beverages are common triggers. According to Sheikh et al. (2023), squamous cell carcinoma is the most common kind of esophageal cancer globally.

1.1. *Worldwide Survey of Esophageal Cancer:*

In terms of cancer-related mortality, esophageal cancer (EC) ranks sixth globally and ninth in terms of incidence, according to studies done by Chen et al. (2023). It's a very deadly illness; EC caused the deaths of nearly 500,000 people worldwide. This incidence is expected to rise by 140% in the world in a period until 2025. The two most prevalent risk factors for EC are drinking liquor & cigarettes. Esophageal cancer of Adenocarcinoma has increased by over 600% in the past three decades. Now it is fast-growing in the Western countries. The ESCC is more dangerous than the EAC (Sheikh et al., 2023).

According to the American Cancer Society, males are more prone than women to acquire EC. The greatest risk is between the ages of 45 and 70, and fewer than 15% of esophageal cancer cases occur in adults younger than 55. According to the survey, the children have an extremely rare chance of getting EC (Huang & Yu, 2018). Although it may range from 5% to 47%, the total five-year rate of recovery suggests that the average mortality ratio for esophageal cancer is 20%. The prognosis for esophageal cancer is better when caught in its earliest, more curable stages. The patient's likelihood of surviving five years is high. The five-year survival rate is a

dismal one percent. According to Lundberg et al. (2022), the average survival duration for individuals with advanced esophageal cancer is barely four to six months.

1.2. *Diagnostic Methods*

Usually, EC does not show any symptoms until it reaches later stages, such as stage 3 or 4. Sometimes the EC is found by mistake due to other medical health problems. The following tests may be used to verify an esophageal detection of cancer;

- Barium swallow study.
- Endoscopy.
- Biopsy.
- CT - Scan.
- MRI Scan.
- Bronchoscopy.
- Endoscopic ultrasound (EUS).
- PET - Scan.
- Thoracoscopy (Sheikh et al., 2023).

2. AI TOOLS IN THE DIAGNOSIS OF ESOPHAGEAL CANCER

2.1. *Chromoendoscopy*

According to Trivedi and Braden (2013), chromoendoscopy helps the endoscopist identify and describe gastrointestinal tract (GIT) lesions. Typically, a range of colors is used to differentiate between normal and abnormal mucosa. By using this technique, endoscopists are encouraged to look more closely and clearly at a particular region of interest. By highlighting the aspects of the mucosal surface topography, chromoendoscopy can enhance the imaging and help to provide detailed information. The provided information helps to make more accurate treatment decisions in the future. The dye can be applied to the GIT surface in the most accurate and regulated way possible using spraying catheters, which create a tiny mist. Because of the potential for aspiration, more care should be taken when coloring the upper Esophagus.

Additionally, there are situations where a foot pump can be helpful, including when patients with inflammatory bowel disease (IBD) need to spray pan colonic dye. When it comes to diagnosing dysplastic lesions in Barrett's esophagus and esophageal cancer, chromoendoscopy has proven to be quite effective (Singh et al., 2020). Chromoendoscopy is a diagnostic technique that makes use of chromogenic reagents as dyes, such as crystal violet, indigo carmine, methylene blue, and Lugol solution (Lauwers & Badizadegan, 2010). Chromoscopy and chromendoscopy are interchangeable terms. According to a 2007 study by Wong Kee Song et al., Lugol's solution is the dye that is most used to detect esophageal squamous cell carcinoma in at-risk individuals.

2.2. *Confocal laser endomicroscopy (CLE)*

One state-of-the-art imaging technique is CLE. The placing of the illumination and collecting systems with an identical focal plane is referred to as "confocal" (Fugazza et al., 2016). It has grown in popularity recently and can be applied to endoscopy. It is commonly referred to as an ocular biopsy for the histological examination of tissue. In CLE, the mucosal surface is illuminated using a blue laser, and any tissue fluorescence that is reflected back is then measured. After the laser has been focused to a specific depth, the light reflecting from the plane can only be refocused using the pinhole confocal hole (Han et al., 2023). The epithelial structures are assessed at a 1000-fold magnification.

CLE comes in two varieties: Two methods of confocal laser endomicroscopy have been developed recently (Vaculová et al., 2022): pCLE and eCLE, which use endoscopes. The limitation of CLE is, it is a single-centre study (Dunbar et al., 2009), and the other primary disadvantages are still the limited field of vision, expensive capital expenditures, and the need for specialized operator training. When used in conjunction with molecular probes, CLE may make it possible to characterize disorders at the molecular level and evaluate how well-focused treatment is working (Dunbar et al., 2009).

3. TREATMENT OF ESOPHAGEAL CANCER

The treatment is given according to the stages of EC that occur in the patients. The various types of treatment options are discussed below.

1. Surgery
    - Esophagogastrostomy.
    - Laparoscopic surgery.
    - Gastrostomy.
    - Esophagectomy (Sheikh et al., 2023).
2. Medical Procedure
    - Chemoradiation therapy.
    - Radiation therapy.
    - Laser therapy.
    - Electrocoagulation.
3. Medications
    - Chemotherapy.
    - Example: cisplatin, 5 5-fluorouracil.
4. New Treatment Options
    - Targeted drug therapy.
    - Example: Pembrolizumab.
    - Immunotherapy.
    - Example: Nivolumab (He et al., 2021).

3.1. *Newer Treatment Options*

3.1.1. *Targeted drug therapy*

To treat cancer, doctors use specific medications or chemicals that specifically target cancer cells and destroy them. Monoclonal antibody therapy is one sort of targeted drug therapy that is used to treat esophageal cancer. Therapeutic applications for laboratory-created monoclonal antibodies include the treatment of cancer and other illnesses. Therapeutic antibodies are an alternative term for monoclonal antibodies. These antibodies will bind to cancer cells or other cells of interest during cancer treatment, promoting the cancer cells' proliferation. According to Sheikh et al. (2023), the linked antibodies can kill cancer cells, halt their progression, or block them from spreading.

Monoclonal antibody infusions are given throughout therapy. According to Sheikh et al. (2023), these methods can be used alone or in combination to target cancer cells directly with radioactive materials, toxins, or drugs. An example of a drug used in targeted drug therapy is Nivolumab.

3.1.1.1 Nivolumab

- Sheikh et al. (2023) state that nivolumab is an IgG4 monoclonal antibody that has been fully humanized. The four parts are composed of two heavy and two light polypeptide chains. There are 440 amino acids in the heavy chain and 214 in each of the two light chains (Sheikh et al., 2023). In 2014, the use of nivolumab (OPDIVO®) was approved by the FDA. On its own, or in combination with chemotherapy based on fluoropyrimidines or platinum, it can be administered to patients. When other treatment options have been exhausted, nivolumab may be the first line of defense against esophageal squamous cell carcinoma that has spread. This kind of medication therapy is targeted.
- **Mechanism:** The medicine stops the signal and prevents the T-cell activation against malignant cells by targeting the anti-PD1 receptor, which is an immunological checkpoint.
- **Pharmacokinetic Parameters: Absorption**: The medication exhibits linear pharmacokinetics, with an area under the curve (AUC) and peak concentration increasing with the dosage. The time taken to reach It takes one to four hours for the plasma concentration to peak.
- **Distribution:** At steady state, the distribution volume is about 6.8 L.
- **Metabolism:** There is currently no systematic study that examines the precise metabolism of nivolumab. The drug's breakdown into smaller peptides and amino acids is merely conjectural at this point.
- **Elimination**: Studies show that nivolumab has a half-life of 25 days; however, the elimination pathway is not yet investigated.
- **ADR**: Common adverse effects are Transitory and manageable. Pneumonitis, interstitial lung disease, respiratory failure, pleural effusion, autoimmune

neuropathy & many more are examples of serious adverse responses. Immune-mediated pneumonitis is one of the uncommon adverse effects.

- **Side effects**: skin rash, itching, facial, lip, or tongue swelling, breathing difficulties, blood in the urine, watery or bloody diarrhea, and discomfort in the abdomen, back discomfort, joint or muscular pain, dry mouth, appetite loss, etc.
- **Dosing**: Nivolumab is infused intravenously for 30 minutes. Doses of 240 mg every two weeks or 480 mg every four weeks are the most typical. (The Sheikh group and colleagues, 2023).
- **Brand Names**: OPDIVO, OPDYTA (Sheikh et al., 2023).
- **Complications produced by the Targeted drug therapy**: Liver problems and confusion, symptoms such as hypertension, oral ulcers, thinning and loss of hair color, etc. (Lupu et al., 2016).

3.1.1.2 Immunotherapy

The goal of immunotherapy is to strengthen the immune system through a series of therapies (Sheikh et al., 2023). Immunotherapy is becoming more popular as a treatment for esophageal cancer. It stimulates the immune system to fight cancer. The body's natural cancer defences are strengthened, guided, or restored by a combination of substances derived from nature and those produced in laboratories. The immune system likely prevents or slows the progression of many cancers by identifying and eliminating abnormal cells. Immunotherapy is administered either by itself or occasionally in conjunction with chemotherapy and radiation treatment. (Sheikh et al., 2023).

- **Immune checkpoint inhibitors**: The medications used in esophageal cancer immunotherapy are known as immune checkpoint inhibitors. The immunological checkpoints are blocked by these medications. The immune system naturally produces these checkpoints, which aid in preventing overly robust immune responses. These medications work by preventing them, which strengthens the immune system's defences against cancer. (Sheikh et al., 2023).
- **T-cell transfer therapy**: Adoptive immunotherapy, T-cell transfer therapy, immune cell therapy, or simply cell therapy is a medical intervention that increases the body's natural ability of T cells to combat cancer. According to Sheikh et al. (2023), one aspect of the treatment involves removing the most effective immune cells from the patient's tumor, modifying them, and then growing them in large quantities in the lab. Eventually, these cells are reintroduced into the patient by a venous needle.
- **Immune system modulators**: Immunomodulators are defined as naturally or synthetically occurring agents. These medications are administered to strengthen the body's immune system against cancer (Sheikh et al., 2023). An example of a drug used as an immunotherapeutic agent is Pembrolizumab.

Pembrolizumab

- Sheikh et al. (2023) described pembrolizumab as a humanized IgG4 kappa antibody. In 2019, pembrolizumab (KEYTRUDA®) was approved as a second-line treatment for certain individuals with localized or metastatic esophageal squamous cell carcinoma by the Food and Drug Administration (FDA). Immunotherapy is what it is.
- **Mechanism**: To prevent an immune response, pembrolizumab blocks the ligands that would deactivate the PD-1 receptor on cells.
- **Pharmacokinetic parameters**: The clearance of pembrolizumab is linear at doses ranging from 0.3 mg/kg up to 10 mg/kg, whereas it is nonlinear at doses below 0.3 mg/kg. Its half-life ranges from 14 to 27.3 days on average. Pembrolizumab takes about 18 weeks to achieve a steady state. It is predicted that pembrolizumab typically has an overall volume of distribution of 2.88–3.48 L.
- **ADR**: The complications associated with infusions, including pneumonitis, hepatitis, renal failure, nephritis, anaphylaxis, and hypersensitivity, which are all caused by the immune system. Pembrolizumab can cause other adverse events that are mediated by the immune system, such as hemolytic anemia, arthritis, and others.
- **Side effects**: skin problems, aches and pains in the back, patches of light skin, lack of appetite, low weight, irregular heartbeats, infections of the urinary and respiratory systems, and arrhythmias.
- **Dosing**: Pembrolizumab is given intravenously as a 200 mg infusion every three weeks and 400 mg every six weeks, 30 minutes after dilution.
- **Brand name**: KEYTRUDA (Sheikh et al., 2023).
- **Complications produced by immunotherapy**: Skin rashes, constipation, poor appetite. Immunotherapy can sometimes trigger an immune response that is too strong, which can lead to inflammation and other immune-related issues (Cappello et al., 2021).

4. BIOMARKERS USED IN ESOPHAGEAL CANCER

Several biomarkers are used for making the treatment decision in Esophageal cancer. Some examples of biomarkers are HER2 amplification, dMMR/MSI-H, and PD-L1 expression (Dhakras et al., 2020).

4.1. *Human Epidermal Growth Factor Receptor 2 (HER2) Amplifications*

In Esophageal cancer, HER2 is a predictive and prognostic biomarker. There are several new HER2-directed drugs being researched for use either alone or in combination, and we anticipate that HER2-directed treatments will have a wider range of applications in the future. (Iqbal & Iqbal, 2014). It inhibits the apoptosis and tumor progression (Prins et al., 2013). Receptor tyrosine kinase 2 for human epidermal growth factor is referred to as ErbB-2 (ERBB2). According to Huang et al.

(2021), when HER2 amplification is administered at high levels, it causes cell membrane proteins to be overexpressed. A tyrosine kinase-like intracellular region, a lipophilic transmembrane domain, and an extracellular ligand-binding domain rich in cysteine make up its three domains. According to Roviello and colleagues (2021).

4.2. *Mismatch Repair Deficiency/Microsatellite Instability (dMMR/MSI-H)*

Genetic recombination occurs during DNA replication in both normal and cancer cells, and mismatch repair systems are crucial for identifying and correcting the bases that are not complementary. Citation: Zhao et al., 2019. For example, microsatellites have been referred to as Simple Sequence Repeats (SSRs) and Short Tandem Repeats (STRs), among many others. Included in it are DNA sequences that repeat from one nucleotide to six. The mismatch repair (MMR) system contains several functional proteins, which help in the rapid response to errors occurring during replication (Zhang et al., 2024). It is a predictive biomarker of immunotherapy (Nádorvári et al., 2024). It helps to predict the surgical, chemotherapeutic, and Results of immunotherapy results for EC treatment (Evaristo et al., 2023).

4.3. *Programmed Death-Ligand 1 (PD-L1)*

According to Bishawi et al. (2021), PD-L1 is a protein that can pass through cell membranes. According to Kim et al. (2016), it is a member of the B7 family. It is a proven positive predictive biomarker that is used to assess how effectively immunotherapy is working in ESCC (Sachdeva et al., 2025). It stops T-cells from becoming tired and stops them from activating. In addition to causing effector T cell death, it hinders cytokine synthesis (Qu et al., 2016). One of the possible reasons for ESCC is PD-L1 expression, which has been linked to HPV infection (Kim et al., 2016).

5. CONCLUSION

In oncology, clinical research regularly produces a new drug to use in chemotherapy protocols. Moreover, EC can be confirmed by performing several tests. The application of AI is growing more common in everyday clinical practice, either directly or indirectly. The newly developed AI tools, such as Chromoendoscopy, Confocal laser endomicroscopy, play an outstanding advanced part in the diagnosis of EC. According to the stages of EC, various treatment options are available, such as surgery, medical procedures, newer treatment options, and chemotherapy. By removing the cancer or slowing or stopping its development, these medicines help patients live longer. Together with radiation therapy, chemotherapy may potentially be a highly effective treatment for EC. These days, immunotherapy and tailored pharmaceutical therapy are crucial treatments for EC control. A medicine used in targeted drug therapy aids in identifying and getting rid of cancer cells. When using targeted medication therapy, monoclonal antibodies are employed. Immunotherapy involves stimulating the patient's immune system to fight cancer. Modulators and inhibitors of immunological checkpoints are used in immunotherapy. Two recently approved medications for targeted drug therapy and immunotherapy are nivolumab

and pembrolizumab. Even though these drugs have ADR & complications too nowadays, it playing an emerging role in the treatment of EC by improving the quality. This review has focused on the function, uses of the biomarkers too.

6. REFERENCES

Allum, W. H., Blazeby, J. M., Griffin, S. M., Cunningham, D., Jankowski, J. A., & Wong, R. (2014). Surgical treatments for esophageal cancers. Annals of the New York Academy of Sciences, 1325(1), 242–268. https://doi.org/10.1111/nyas.12533

Arnal, M. J. D. (2015). Esophageal cancer: Risk factors, screening and endoscopic treatment in Western and Eastern countries. World Journal of Gastroenterology, 21(26), 7933. https://doi.org/10.3748/wjg.v21.i26.7933

Bishawi, M., Bowles, D., Ploth, T., Melendez, J., & Force, S. (2021). PD-1 and PD-L1 expression. Cardiovascular Pathology, 54, 107331. https://doi.org/10.1016/j.carpath.2021.107331

Cappello, G., Calabrese, C., Capone, P., Spada, C., & Laghi, L. (2021). Gastrointestinal adverse events of immunotherapy. BJR|Open, 3(1), 20210027. https://doi.org/10.1259/bjro.20210027

Chen, R., Liu, Y., Song, G., Li, B., Zhao, D., & Zheng, Z. (2023). Patterns and trends in esophageal cancer incidence and mortality in China: An analysis based on cancer registry data. Journal of the National Cancer Center, 3(1), 21–27. https://doi.org/10.1016/j.jncc.2023.01.001

Dhakras, P., Uboha, N., Horner, V., Reinig, E., & Matkowskyj, K. A. (2020). Gastrointestinal cancers: Current biomarkers in esophageal and gastric adenocarcinoma. Translational Gastroenterology and Hepatology, 5, 55. https://doi.org/10.21037/tgh.2019.12.06

Drug Discovery in Japan: Investigating the Sources of Innovation. (2019). Springer Singapore. https://doi.org/10.1007/978-981-13-8906-1

Dunbar, K. B., Okolo, P., Montgomery, E., & Canto, M. I. (2009). Confocal laser endomicroscopy in Barrett's esophagus and endoscopically inapparent Barrett's neoplasia: A prospective, randomized, double-blind, controlled, crossover trial. Gastrointestinal Endoscopy, 70(4), 645–654. https://doi.org/10.1016/j.gie.2009.02.009

Evaristo, G., Sepulveda, A., Pinto, J., Nobre, M., Afonso, L. P., & Oliveira, P. (2023). Relation between mismatch repair status, chemoresponse, survival and anatomic location in gastroesophageal adenocarcinoma. Canadian Journal of Surgery, 66(1), E79–E87. https://doi.org/10.1503/cjs.010122

Fang, P., Chen, Y., Zhang, Z., Wang, Y., & Chen, Z. (2022). Immunotherapy resistance in esophageal cancer: Possible mechanisms and clinical implications. Frontiers in Immunology, 13, 975986. https://doi.org/10.3389/fimmu.2022.975986

Flynn, J. P., & Gerriets, V. (2023, June 26). Pembrolizumab. In StatPearls [Internet]. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK546616/

Fugazza, A., Gaiani, F., Carra, M. C., Brunetti, F., Lévy, M., Sobhani, I., Azoulay, D., Catena, F., & de'Angelis, G. L. (2016). Confocal laser endomicroscopy in gastrointestinal and pancreatobiliary diseases: A systematic review and meta-analysis. BioMed Research International, 2016, 1–31. https://doi.org/10.1155/2016/4638683

Han, W., Li, Y., Zhang, Y., Wang, X., & Li, L. (2023). Confocal laser endomicroscopy for detection of early upper gastrointestinal cancer. Cancers, 15(3), 776. https://doi.org/10.3390/cancers15030776

He, S., Xu, J., Liu, X., & Zhen, Y. (2021). Advances and challenges in the treatment of esophageal cancer. Acta Pharmaceutica Sinica B, 11(11), 3379–3392. https://doi.org/10.1016/j.apsb.2021.03.008

Huang, F.-L., & Yu, S.-J. (2018). Esophageal cancer: Risk factors, genetic association, and treatment. Asian Journal of Surgery, 41(3), 210–215. https://doi.org/10.1016/j.asjsur.2016.10.005

Huang, H.-Y. (2013). Cancer: Epidemiology of gastrointestinal cancers other than colorectal cancers. In B. Caballero (Ed.), Encyclopedia of Human Nutrition (pp. 253–258). Elsevier. https://doi.org/10.1016/B978-0-12-375083-9.00037-4

Huang, H., Wang, Z., Li, Y., Zhao, Q., & Niu, Z. (2021). Amplification of the human epidermal growth factor receptor 2 (HER2) gene is associated with a microsatellite stable status in Chinese gastric cancer patients. Journal of Gastrointestinal Oncology, 12(2), 377–387. https://doi.org/10.21037/jgo-20-540

Ikeda, G., Miyakoshi, J., Yamamoto, S., & Kato, K. (2024). Nivolumab in unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma. Future Oncology, 20(7), 665–677. https://doi.org/10.2217/fon-2023-0621

Iqbal, N., & Iqbal, N. (2014). Human epidermal growth factor receptor 2 (HER2) in cancers: Overexpression and therapeutic implications. Molecular Biology International, 2014, 1–9. https://doi.org/10.1155/2014/852748

Kharkar, P. B., Talkar, S. S., Kadwadkar, N. A., & Patravale, V. B. (2017). Nanosystems for oral delivery of immunomodulators. In A. M. Grumezescu (Ed.), Nanostructures for Oral Medicine (pp. 295–334). Elsevier. https://doi.org/10.1016/B978-0-323-47720-8.00012-2

Kim, R., Keam, B., Kwon, D., Ock, C.-Y., Kim, M., Kim, T. M., Kim, D.-W., Heo, D. S., & Lee, J. (2016). Programmed death ligand-1 expression and its prognostic role in esophageal squamous cell carcinoma. World Journal of Gastroenterology, 22(36), 8389–8397. https://doi.org/10.3748/wjg.v22.i36.8389

Lao, Y., Shen, D., Zhang, W., He, R., & Jiang, M. (2022). Immune checkpoint inhibitors in cancer therapy—How to overcome drug resistance? Cancers, 14(15), 3575. https://doi.org/10.3390/cancers14153575

Lauwers, G. Y., & Badizadegan, K. (2010). New endoscopic techniques: Challenges and opportunities for surgical pathologists. Surgical Pathology Clinics, 3(3), 411–428. https://doi.org/10.1016/j.path.2010.05.001

Lundberg, E., Lagergren, P., Mattsson, F., & Lagergren, J. (2022). Life expectancy in survivors of esophageal cancer compared with the background population. Annals of Surgical Oncology, 29(5), 2805–2811. https://doi.org/10.1245/s10434-021-11141-4

Lupu, I., Voiculescu, V. M., Bacalbasa, N., Prie, A.-M., Cozma, C. N., Dumitrescu, M., Giurcaneanu, C., & Caruntu, C. (2016). Cutaneous complications of molecular targeted therapy used in oncology. Journal of Medicine and Life, 9(1), 19–25.

Mikuni, H., Yamamoto, S., & Kato, K. (2021). Nivolumab for the treatment of esophageal cancer. Expert Opinion on Biological Therapy, 21(6), 697–703. https://doi.org/10.1080/14712598.2021.1897102

Mühr-Wilkenshoff, F., Stahl, M., Faiss, S., Zeitz, M., & Scherübl, H. (2004). Aktuelle Diagnostik und Therapie des Ösophaguskarzinoms. Zeitschrift für Gastroenterologie, 42(06), 615–621. https://doi.org/10.1055/s-2004-813178

Nádorvári, M. L., Lotz, G., Kulka, J., Kiss, A., & Tímár, J. (2024). Microsatellite instability and mismatch repair protein deficiency: Equal predictive markers? Pathology & Oncology Research, 30, 1611719. https://doi.org/10.3389/pore.2024.1611719

Pilonis, N. D., Januszewicz, W., & di Pietro, M. (2022). Confocal laser endomicroscopy in gastro-intestinal endoscopy: Technical aspects and clinical applications. Translational Gastroenterology and Hepatology, 7, 7. https://doi.org/10.21037/tgh-20-235

Prins, M. J. D., Ruurda, J. P., Van Diest, P. J., Van Hillegersberg, R., & Ten Kate, F. J. W. (2013). The significance of the HER-2 status in esophageal adenocarcinoma for survival: An immunohistochemical and an in situ hybridization study. Annals of Oncology, 24(5), 1290–1297. https://doi.org/10.1093/annonc/mds619

Qu, H.-X., Zhao, L.-P., Zhan, S.-H., Geng, C.-X., Xu, L., Xin, Y.-N., & Jiang, X.-J. (2016). Clinicopathological and prognostic significance of programmed cell death ligand 1 (PD-L1) expression in patients with esophageal squamous cell carcinoma: A meta-analysis. Journal of Thoracic Disease, 8(11), 3197–3204. https://doi.org/10.21037/jtd.2016.11.75

Rendon, A., & Rayi, A. (2024, February 28). Nivolumab. In StatPearls [Internet]. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK567801/

Roviello, G., Aprile, G., D'Angelo, A., Roviello, F., & Nobili, S. (2021). Human epidermal growth factor receptor 2 (HER2) in advanced gastric cancer: Where do we stand? Gastric Cancer, 24(4), 765–779. https://doi.org/10.1007/s10120-021-01184-7

Sachdeva, M., Agarwal, S., Gandhi, A., Choudhary, M. C., & Choudhury, A. (2025). PD-L1 expression as a negative predictive biomarker in advanced esophageal squamous-cell cancer treated with chemotherapy alone. ESMO Gastrointestinal Oncology, 7, 100109. https://doi.org/10.1016/j.esmoop.2025.100109

Sheikh, M., Roshandel, G., McCormack, V., & Malekzadeh, R. (2023). Current status and future prospects for esophageal cancer. Cancers, 15(3), 765. https://doi.org/10.3390/cancers15030765

Singh, R., Jayanna, M., Wong, J., Ho, S., & Uedo, N. (2020). Chromoendoscopy: Role in modern endoscopic imaging. Translational Gastroenterology and Hepatology, 5, 39. https://doi.org/10.21037/tgh.2019.12.10

Tilak, T. V. S. V. G. K., Patel, A., & Kapoor, A. (2023). Molecular basis and clinical application of targeted therapy in oncology. Medical Journal Armed Forces India, 79(2), 128–135. https://doi.org/10.1016/j.mjafi.2021.05.007

Trivedi, P. J., & Braden, B. (2013). Indications, stains and techniques in chromoendoscopy. QJM: An International Journal of Medicine, 106(2), 117–131. https://doi.org/10.1093/qjmed/hcs190

Vaculová, J., Šafanda, M., Švec, J., & Kala, Z. (2022). The use of confocal laser endomicroscopy in diagnosing Barrett's esophagus and esophageal adenocarcinoma. Diagnostics, 12(7), 1616. https://doi.org/10.3390/diagnostics12071616

Wang, H., Xu, Y., Zuo, F., Liu, J., & Yang, J. (2022). Immune-based combination therapy for esophageal cancer. Frontiers in Immunology, 13, 1020290. https://doi.org/10.3389/fimmu.2022.1020290

Wang, Y., Mukkamalla, S. K. R., Singh, R., & et al. (2024, August 17). Esophageal cancer. In StatPearls [Internet]. StatPearls Publishing.

Want, M. Y., Bashir, Z., & Najar, R. A. (2023). T cell based immunotherapy for cancer: Approaches and strategies. Vaccines, 11(5), 835. https://doi.org/10.3390/vaccines11050835

Wong Kee Song, L. M., Adler, D. G., Chand, B., Conway, J. D., Croffie, J. M. B., Disario, J. A., Mishkin, D. S., Shah, R. J., Somogyi, L., Tierney, W. M., & Petersen, B. T. (2007). Chromoendoscopy. Gastrointestinal Endoscopy, 66(4), 639–649. https://doi.org/10.1016/j.gie.2007.05.029

Zahavi, D., & Weiner, L. (2020). Monoclonal antibodies in cancer therapy. Antibodies, 9(3), 34. https://doi.org/10.3390/antib9030034

Zhang, Z., Li, X., Wang, Y., & Zhang, Q. (2024). Microsatellite instability in gastric cancer: Molecular features and clinical implications. Clinical and Translational Discovery, 3(1), 12. https://doi.org/10.1002/ctd2.12

Zhao, P., Li, L., Jiang, X., & Li, Q. (2019). Mismatch repair deficiency/microsatellite instability-high as a predictor for anti-PD-1/PD-L1 immunotherapy efficacy. Journal of Hematology & Oncology, 12(1), 54. https://doi.org/10.1186/s13045-019-0738-1